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(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.

## Description

## NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

## **BACKGROUND OF THE INVENTION**

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

#### 35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEO ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 10 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 15 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 20 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 25 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 15 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an 25 even integer from 2 to 422; and a transcription terminator. embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 30 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 35 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computer-readable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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## DETAILED DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract. protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag™ peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide. thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc.

15 Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (*Nuc. Acids Res.* 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example,  $\alpha$ -globin,  $\beta$ -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

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The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

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A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436. Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, *Nuc. Acids Res.* 14:4683, 1986) are not always exact and may vary by as much as  $\pm$  5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

# Table 1

<u>Protein</u>	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	. 18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	. 25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	. 24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	· 21
AFP8766	78	15
AFP397185	80	20
AFP195042	. 82	21
AFP310695	84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	17
AFP356885	130	17
AFP226938	132	16
AFP138504	134	29
AFP359196	136	24
AFP501809	138	27
AFP152733	140	15
AFP541394	142	23
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	20
AFP257336	152	. 25
AFP195800	154	23
AFP179530	156	. 19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	
AFP325761	164	16
AFP226024	166	22
AFP257094	168	22
AFP197103	170	27 27
AFP271855	170	
AFP324816		17
AFP407963	174 176	29 25
AFP369635	176	25
AFP93743	178	17
AFP243230	180	28
<del>-</del>	182	15
AFP169316	184	21
AFP130852	186	15

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AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	-25
AFP425535	212	25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270	16
AFP275580	272	28
AFP298054	274	21
AFP348226	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19

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AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968,	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	. 26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	· 29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	. 24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	. 25
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AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27
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A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

6         AFP413680         234         AFP117501           12         AFP178828         236         AFP194554           18         AFP477303         240         AFP313600           24         AFP177000         242         AFP262739           42         AFP199200         252         AFP250422           48         AFP326051         254         AFP198645           66         AFP324422         258         AFP460626           68         AFP374312         270         AFP266188           72         AFP74517         272         AFP275580           90         AFP345861         288         AFP236718           92         AFP395942         294         AFP280451           96         AFP297548         300         AFP277451           98         AFP188135         306         AFP138740           110         AFP404202         324         AFP195562           134         AFP138504         338         AFP229269           138         AFP501809         342         AFP237679           156         AFP179530         344         AFP239397           162         AFP24615         350         AFP306591	SEQ ID NO:	Protein	SEQ ID NO:	Protein
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92         AFP395942         294         AFP280451           96         AFP297548         300         AFP277451           98         AFP188135         306         AFP138740           110         AFP404202         324         AFP195562           134         AFP138504         338         AFP229269           138         AFP501809         342         AFP237679           156         AFP179530         344         AFP249599           158         AFP279267         348         AFP290397           162         AFP244615         350         AFP306591           164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186-         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	72	AFP74517	272	AFP275580
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110         AFP404202         324         AFP195562           134         AFP138504         338         AFP29269           138         AFP501809         342         AFP237679           156         AFP179530         344         AFP249599           158         AFP279267         348         AFP290397           162         AFP244615         350         AFP306591           164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	98	AFP188135	306	AFP138740
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156         AFP179530         344         AFP249599           158         AFP279267         348         AFP290397           162         AFP244615         350         AFP306591           164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	134	AFP138504	338	AFP229269
158         AFP279267         348         AFP290397           162         AFP244615         350         AFP306591           164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	' 138	AFP501809	342	AFP237679
162         AFP244615         350         AFP306591           164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	156	AFP179530	344	AFP249599
164         AFP325761         366         AFP347179           174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	158	AFP279267	348	AFP290397
174         AFP324816         374         AFP372822           180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	162	AFP244615	350	AFP306591
180         AFP93743         378         AFP375952           204         AFP137186         386         AFP404279           206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	164	AFP325761	366	AFP347179
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206         AFP127023         396         AFP436666           210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	180	AFP93743	378	AFP375952
210         AFP293220         398         AFP448623           224         AFP561930         408         AFP545268	204	AFP137186 <sup>-</sup>	386	AFP404279
224 AFP561930 408 AFP545268	206	AFP127023	396	AFP436666
111313200	210	AFP293220	398	AFP448623
230 AFP199044 416 AFP71288	224	AFP561930	408	AFP545268
	230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

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AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and anti-viral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., J. Biol. Chem. 227:5784-5789, 1996).

This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

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Table 3

<del></del>	Table 3
Locus	Accession Number & Description
AFP130852	AE003823 (fly genomic)
AFP169968	AE003515 (fly genomic)
AFP174843	AF283518 (Mus musculus elongation factor sec)
AFP176427	AE003808 (fly genomic)
AFP178828	PSN_V61483
AFP179530	AE003708 (fly genomic)
AFP188135	AE003677 (fly genomic)
AFP195042	PIR_T41241 (yeast oxysterol-binding protein family)
AFP198645	AE003718 (fly genomic)
AFP199200	AF113691 (human clone FLB4739 PRO1238 mRNA)
AFP204736	AC069237 (human chromosome 3 clone RP11-175M9)
AFP229269	AF247177 (Mus musculus sphingosine-1-phosphate
	phosphohydrolase)
AFP230872	AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AFP279267	AE003559 (fly genomic)
AFP347179	AE003499 (fly genomic) Z1041035F6P
AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP359196	AE003530 (fly genomic)
AFP374312	AE003538 (fly genomic)
AFP389687	AE003831 (fly genomic)
AFP395942	AB041564 (mouse brain cDNA; clone MNCb-0914)
AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP477303	AE003778 (fly genomic)
AFP62060	PSP_Y94938 (Human secreted protein clone ye78_1)
AFP71288	AL161655 (human chromosome 20 clone RP11-116E13)
AFP74517	PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
	113 Cooo13 (itumaii nucleoside diphosphate kinase nomolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone:RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

Locus	Accession Number & Description
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology
	to PSP_W35393 Human TB2 gene product)
AFP202885	AB037808 (human mRNA for KIAA1387 protein)
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)
AFP250422	AF208849 (human BM-007 mRNA)
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to
	major facilitator protein homolog, fission yeast: PIR_S62432)
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak
	homology to dinitrogenase reductase activating glycohydrolase (draG)
	Archaeoglobus fulgidus: PIR_C69465)
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on
	chromosome 10. Contains a novel gene and the 5' end of the gene for a
	novel protein; ortholog of mouse FISH protein)
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:
	Human O-linked GlcNAc transferase mRNA)

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to *E. coli*  $\beta$ -galactosidase (1,021 residues; see Casadaban et al., *J. Bacteriol.* 143:971-980, 1980), a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

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As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

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are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

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Nucleotide Resolutions Resolutions Complement T T Α Α C C G G G G  $\mathbf{C}$ C T T Α Α R AG. Y C|T Y C|T R AIG M A|C K G|TK GIT A|C M S C|G S C|GW A|TA|TW Н A|C|T D A|G|T CGT В V A|C|G V **AICIG** C|G|T В D A|G|T Η A|C|T N **AICIGIT** N A|C|G|T

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Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter		Degenerate
Acid	Code	Codons	Codon
Cys	С	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	Α	GCA GCC GCG GCT	GCN
Gly	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	Н	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTC TTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	•	TAA TAG TGA	TRR
Asn Asp	В		RAY
Glu Gln	Z		SAR
Any	X		NNN
Gap	-		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

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exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

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## Table 8

AFP152733	K562 cells
AFP169796	T-cells
AFP173341	testis
AFP17588	fetal liver or spleen
AFP194554	fetal liver or spleen
AFP199922	testis
AFP229269	placenta
AFP237679	fetal liver or spleen
AFP257094	adult brain
AFP258118	epidermal breast keratinocytes
AFP263430	breast
AFP276202	infant brain
AFP287436	testis
AFP290397	testis
AFP306591	fetal heart
AFP325761	K562 cells
AFP352125	testis
AFP359138	infant brain
AFP369635	germinal center B-cells
AFP409112	kidney
AFP483037	neonatal keratinocytes
AFP49026	peripheral blood eosinophils of asthma patients
AFP545268	K562 cells
AFP561930	fetal liver or spleen
AFP62060	testis
AFP62197	pregnant uterus
AFP93743	germinal center B-cells
AFP98983	fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex Taq<sup>TM</sup>; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or Advantage<sup>TM</sup> 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

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Table 9, continued

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Tissues screened were: 1, brain; 2, heart; 3, kidney; 4, liver; 5, lung; 6, pancreas; 7, placenta; 8, skeletal muscle; 9, colon; 10, ovary; 11, peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H<sub>2</sub>O; 22, genomic DNA. Y=yes; n=no; nd=not determined.

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Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

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Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of 15 interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

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Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable),digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells 15 include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982). DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 20 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

Insect cells can be infected with recombinant baculovirus, commonly derived from Autographa californica nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, 15 Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols, Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposonbased system described by Luckow et al. (J. Virol. 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, J. Gen. Virol. 71:971-976, 1990; Bonning et al., J. Gen. Virol. 75:1551-1556, 1994; and Chazenbalk and Rapoport, J. Biol. Chem. 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells. 25 typically a cell line derived from the fall armyworm, Spodoptera frugiperda (e.g., Sf9 or Sf21 cells) or Trichoplusia ni (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial 30 suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10<sup>5</sup> cells to a density of 1-2 x 10<sup>6</sup> cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, ibid.; O'Reilly et al., ibid.; Richardson, ibid.). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. 15 Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (Bangalore) 11:47-58, 1987.

Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

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Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally 15 include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

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Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

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Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, *Chem. Pept. Prot.* 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the Cytosensor<sup>TM</sup> Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as 20 compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

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Assays measuring cell proliferation or differentiation are well known in For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., Investigational New Drugs 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, Methods Enzymol. 109:749-773, 1985; Wahl et al., Mol. Cell Biol. 8:5016-5025, 1988; and Cook et al., Analytical Biochem. 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., J. Immunol. Methods 82:169-179, 1985), and use of tetrazolium salts (Mosmann, J. Immunol. Methods 65:55-63, 1983; Alley et al., Cancer Res. 48:589-601, 1988; Marshall et al., Growth Reg. 5:69-84, 1995; and Scudiero et al., Cancer Res. 48:48274833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

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In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO<sub>2</sub> atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. <sup>3</sup>H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, *J. Immunol. Methods* 120:271-276, 1989; Greenfeder et al., *J. Biol. Chem.* 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as <sup>3</sup>H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, *ibid.*).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using <sup>3</sup>H-proline incorporation into nascent secreted collagen. <sup>3</sup>H-labeled collagen is visualized by

SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1 $\beta$  and TNF $\alpha$  levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

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Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can 15 assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (J. Biol. Chem. 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately 10<sup>4</sup> - 10<sup>5</sup> cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. 183:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

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Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 $\alpha$  or IL-1 $\beta$  is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g.,  $\gamma$  counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol.* 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol.* 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACore<sup>TM</sup>, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant  $K_i$  is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin 15 (Steiner et al., J. Biol. Chem. 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal-human plasma; Dennis et al., J. Biol. Chem. 270:25411-25417, 1995).

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Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, J. Exp. Med. 151:1232-1243, 1980; Schwartz et al., J. Clin. Invest. 67:1650-1658, 1981). As disclosed by Anderson et al. (Proc. Natl. Acad. Sci. USA 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (Thrombosis Res. 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, Methods Enzymol. 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

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Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., J. Biol. Chem. 263:14621-14624, 1988; Wu et al., J. Biol. Chem. 267:963-967, 1992; and Johnston and Tang, Meth. Cell Biol. 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition *in vivo*. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, *Brit. J. Dermatol.* 

118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB4 levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton 20 et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO<sub>2</sub>/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

35 Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine* 

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). A test substance is injected subcutaneiously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to 25 limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness 15 excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, Advan. Enzyme Regul. 35:293-301, 1995; Conway et al., Clin. Exp. Metastasis 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, Semin. Thromb. Hemost. 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEO ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002. 1984.

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Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Ta</u>	<u>ble 10</u>		
<u>Protein</u>		Hexa	peptide N	<u>-termini</u>	
AFP210015	389	405	97	388	359
AFP170681	51	334	113	49	140
AFP413680	221	207	220	206	198
AFP483037	219	218	82	216	215
AFP230872	189	188	73	156	68
AFP178828	211	210	209	208	207
AFP200134	150	149	146	132	145
AFP195796	99	97	111	208	240

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	.284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	. 32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66 -	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	. 64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	. 2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23	238	363	224
AFP229039	226	91	116	161	225.
AFP176297	261	382	183	119	182
AFP356885	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

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AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182.	216	43
AFP127023	86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

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AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	. 592	591	374	525
AFP75785	128	127	136	99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	118	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186 .	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')<sub>2</sub> and Fab fragments, single chain antibodies, and the like, including genetically engineered antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

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Alternative techniques for generating or selecting antibodies useful herein include *in vitro* exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K<sub>a</sub>) of 10<sup>6</sup> M<sup>-1</sup> or greater, preferably 10<sup>7</sup> M<sup>-1</sup> or greater, more preferably 10<sup>8</sup> M<sup>-1</sup> or greater, and most preferably 10<sup>9</sup> M<sup>-1</sup> or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, *Ann. NY Acad. Sci.* 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity in vitro and in vivo.

The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, *Pseudomonas* exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

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Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 15 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., *ibid.*, ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, the **OMIM<sup>TM</sup>** Database, **Johns Hopkins** University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

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Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

			Ta	Table 11			
AFP	GenBank Acc. No.	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
AFP127023	AP001155	RP11-594B10	*	18	18q12	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	Ξ	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	15	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	15		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11- 116N21;RP11-7F17	*	14	14q23.3	62132030	62313415
AFP179530	AC011475	CTC-539A10	*	12	12q12	41234876	41456630
AFP188135	AC013740	*	*	6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	16	16q22.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	91	16q11.2	44574019	44904017
AFP199200	CNS01DV7	BAC-R-1070N10	*	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14q21.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	569709	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055 3	3	3q13.12	116466893	116517043
AFP249599	AL157714	RP11-541H12	*	_	1q22-23.3	161893354	162136704
AFP250422	AC012046	RP11-312P12	*	10	10q22.1	81289799	81650062
AFP262739	AC005884	hRPK.264_B_14	*	17	17q23.3	64245127	64365313
AFP275580	AC016773	*	*	3	3q21.3	141329005	141513510
AFP277451	AC055822	RP11-707M3	*	8	8q13.3	75395740	75583383
AFP279267	*	*	A1566086	01	1.11p01	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	01	10q24.32	115276306	115467187
AFP290397	*	*	AA421069	15	15q15,3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	*	W52728	11	11911	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP325761	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

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20153358	44286594	126134148	138765140	128134589	3500834	4222465	143641730	1514256	59940397	19003942	173547400	70471703	16677574	50564907	60714738	108794286	137478427	*	77633569
19959493	44087441	125918909	138667522	128134250	3479999	4189155	142961410	1512179	8892686	18993217	173540737	70222075	16491516	50554924	60450247	108494503	137477811	*	77419530
14p11.1	17q21.2	12q24.23	1912-21.2	11923.3	16p13.3	16p13.3		4p16.3	19q13.33	8p21.3	5q33.1	16q22.1	19p13.13	6p21.1	13q21.1	13q34	6q22.33	1p35.1-36.13	4q21.22
14	17	12	_	=	16	16	7	4	19	∞	5	16	19	9	13	13	9	1	4
AI525611	*	#	*	AI253088	AI741157	*	AI133727	AI341602	*	AI814257	AI140615	*	#	AW583171	#	*	AA493506	*	*
BAC-R-407N17	CTD-2534121	*	3.28E+21	*	*	*	*	*	cosmid-R31181	*	*	RP11-502K10	CTB-5E10	*	RP11-342J4	RP11-391H12	*	RP5-1056L3	RP11-791G16
AL132639	AC015936	AC025740	AL022240	*	*	AC004235	*	*	AC006942	*	*	AC009131	AC008686	*	AL138695	AL136221	*	HS1056L3	AC067942
AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517	AFP93743

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

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The bioactive conjugates described herein can be delivered intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDraw<sup>TM</sup> (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds, x-ray crystallography to determine the three-dimensional structure in atomic detail, nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

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students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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### **EXAMPLES**

## Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His<sub>6</sub> tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique Smal site just downstream of the MBP-His<sub>6</sub>-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of Smal-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura<sup>+</sup> transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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## Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (*ibid.*). 100-ml cultures in minimal glucose media containing casamino acids and 100  $\mu$ g/ml ampicillin are grown at 37°C in 500-ml baffled flasks to OD<sub>600</sub>  $\approx$  0.5. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at -70°C.

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## Example 3

For larger-scale protein preparation, 500-ml cultures of  $E.\ coli$  BL21 expressing the AFP-MBP-His<sub>6</sub> fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH<sub>2</sub>PO<sub>4</sub>, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2  $\mu$ g/ml Leupeptin, 2  $\mu$ g/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

# Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with Smal, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (*S. cerevisiae*) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H<sub>2</sub>O]) and incubated at 30°C. After about 48 hours, the Ura<sup>+</sup> yeast

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transformants from a single plate are resuspended in 1 ml  $H_2O$  and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300  $\mu$ l acid-washed glass beads and 200  $\mu$ l phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600  $\mu$ l ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10  $\mu$ l  $H_2O$ .

Transformation of electrocompetent *E. coli* host cells (Electromax DH10B<sup>TM</sup> cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% Bacto<sup>TM</sup> Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl<sub>2</sub>, 10 mM MgSO<sub>4</sub>, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% Bacto<sup>TM</sup> Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO<sub>2</sub>, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (Lipofectamine<sup>TM</sup> Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

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mixed with 605 μl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 μM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

#### **CLAIMS**

#### We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEQ ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

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- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:

a transcription promoter;

a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and

a transcription terminator.

- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- 14. A method of producing a polypeptide comprising culturing the cell of claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
  - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

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a transcription promoter;

a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.

- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

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17

•	_	•	_	-	_	tta Leu					-			528
						aca Thr								576
			-	_		ctt Leu	-		_		-		-	624
-						gac Asp 215	-							672
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	130					135					140					
Ser 145		Met	Ile	Gly	Val 150		Pro	Cys	Ile	Asp 155	Lys	Ser	Val	Met	Glu 160	
Ser	Ser	Asp	Arg	Cys 165	Ala	Leu	Ser	Ser	Pro 170	Ser	Leu	Ala	Phe	Thr 175	Pro	
Pro	Пe	Lys	Thr 180	Leu	Gly	Thr	Pro	Thr 185	Gln	Pro	Gly	Ser	Thr 190	Pro	Arg	
Ile	Ser	Thr 195	Met	Arg	Pro	Leu	A1a 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	He	Ser	Asp 215	Arg	Gln	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	
Leu 225	Val	Ser	Lys	Ala	Met 230	Glu	Tyr	Met	Phe	G1y 235	Trp					
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-				-					tct Ser							96
									gac Asp							144
	-			-	-	-	_		atg Met					-		192
	-	-		_	-	_		_	aat Asn						_	240

19

											gaa Glu			_		288
•			-	-	-		-				cca Pro	-		_		336
		-		_			-				gat Asp		-	_	_	384
-	-										att Ile 140	_			-	432
				_			_				gaa G1u	-		_		480
	-			-			-	_			tcc Ser			-		528
			-		-					-	ttg Leu	-		-		576
_	_		-	-			-		_		cct Pro					624
	aag Lys 210		taa *													636
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Asp	Gln	Met 35	Ser	Asn	Glu	Glu	Leu 40	Tyr	Asp	Asn	Ļeu	Leu 45		Cys	Ser		
His	Arg 50	Thr	His	۷a٦	Val	A1 a 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	Asp	Leu		
65			Glu		70					75					80		
			Ser	85					90					95	_		
			Ser 100					105					110				
		115	Val				120					125					
	130		Glu	*		135					140						
145			Leu		150					155				•	160		
			Ser	165					170					175			
			Ala 180					185					190				
	Lys Lys 210	195	Lys	Asp	Tyr	Leu	G1n 200	Ile	Leu	Arg	Pro	Asn 205	Ile	Ile	Lys	** *	
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		11>															
			Homo	sap	oiens	5											
		20>	CDC													٠	
		21> 22>	(1).	(6	551)										٠		
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cct Pro	ccg Pro	ccg Pro	ccc Pro	cca Pro	cct Pro	ctg Leu	gga Gly	ccc Pro	cat His	tcc Ser	aac Asn	cgg Arg	acc Thr	acc Thr	cca Pro		96

	20			25				30				
	Ala		aac Asn			_	-	-		atg Met		144
			ggc Gly 55									192
			gcg Ala									240
			ccg Pro								•	288
			gtg Val								;	336
			ccc Pro						_	-	;	384
			tgc Cys 135								4	432
			cct Pro								4	480
			atc Ile								į	528
			aaa Lys								Ę	576
			gaa Glu								6	524

22

195 200 205

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<210> 12

<211> 216

<212> PRT

<213> Homo sapiens

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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro 65 70 . 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro 100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val 165 170 175

Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro 180 185 190

Trp Ala Phe Met Gln Gly Glu Ile Ala Thr Ile Leu Ala Gly Asp Val 195 200 205

Lys Val Lys Lys Glu Arg Asp Pro 210 215

<210> 13

<211> 468

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24

468

48

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                                25
Leu Thr Lys Phe Asn Lys Glu Asn Asn Cys Val Leu Pro His Ser Lys
Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
                        55
                                            60
Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro
65
                    70
                                        75
Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
                                    90
Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr
                                105
Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
        115
                            120
                                                125
Val Phe Leu Glu Leu Lys Asp Gly Gln Gln Ilé Pro Val Phe Lys Leu
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1				5					10					15		
												aca Thr				96
_					-				_		-	ttt Phe 45	-			144
	_			_								tgg Trp				192
		-	_	-		-					_	ctg Leu				240
	_			-				-	-			cac His		_	-	288
											_	cag Gln	-	-	-	336
												ggc Gly 125				384
_	_		_	_	_		-	_	-	_		cag Gln			_	432
												acc Thr				480
_			-	_		_	_			-		cgc Arg		_		528
						-				_		gga Gly	-	_		576

26

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180 185 190 gcc ctg agt cta agg tcc agc aca aac ccg gca gat tcc cgg aca gag 624 Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 195 200 205 get tet gag gat gae atg gga gae aaa get eec aag agg gee aaa eec 672 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 210 215 220 atc aaa aaa gcg ccc aaa gct gag cca ctg gct tcc aag aca ctg aag 720 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 225 230 240 acc cgg ccc aag aag acc tct ggc ggg ggc gac tca gct tga 765 Thr Arg Pro Lys Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala \* 245 250 <210> 16 <211> 254 <212> PRT <213> Homo sapiens <400> 16 Met Val Ser Trp Ile Ile Ser Arg Leu Val Val Leu Ile Phe Gly Thr 5 10 Leu Tyr Pro Ala Tyr Ser Ser Tyr Lys Ala Val Lys Thr Lys Asn Val Lys Glu Tyr Val Lys Trp Met Met Tyr Trp Ile Val Phe Ala Phe Phe Thr Thr Ala Glu Thr Leu Thr Asp Ile Val Leu Ser Trp Phe Pro Phe 55 Tyr Phe Glu Leu Lys Ile Ala Phe Val Ile Trp Leu Leu Ser Pro Tyr 75 80 Thr Lys Gly Ser Ser Val Leu Tyr Arg Lys Phe Val His Pro Thr Leu 90 Ser Asn Lys Glu Lys Glu Ile Asp Glu Tyr Ile Thr Gln Ala Arg Asp 105 Lys Ser Tyr Glu Thr Met Met Arg Val Gly Lys Arg Gly Leu Asn Leu 125 120 Ala Ala Asn Ala Ala Val Thr Ala Ala Ala Lys Gly Gln Gly Val Leu 130 135 Ser Glu Lys Leu Arg Ser Phe Ser Met Gln Asp Leu Thr Leu Ile Arg

145		۸۵۸	۸٦٠	Lou	150		Cln	Λησ	Dno	155		۸۵۵	Lou	۸۰۰۰	160	
АЅР	Giu	ASP	Ald	165	Pro	Leu	uIII	Arg	170	АЅР	Gly	Arg	Leu	Arg 175	Pro	
Ser	Pro	Gly	Ser 180	Leu	Leu	Asp	Thr	Ile 185	Glu	Asp	Leu	Gly	Asp 190	Asp	Pro	
Ala	Leu	Ser 195	Leu	Arg	Ser	Ser	Thr 200	Asn	Pro	Ala	Asp	Ser 205	Arg	Thr	Glu	
Ala	Ser 210	Glu	Asp	Asp	Met	Gly 215	Asp	Lys	Ala	Pro	Lys 220	Arg	Ala	Lys	Pro	
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				Α,Τ,		^ G								-		
.+.		100>			_4_	<b>.</b>			_4_						_4_	40
											gga Gly					48
											acc Thr					96
att	atc	qcc		cac	cat	aac	att	ccc	ttc	tac	gtg	act		ccc	agc	144
											Val					
											gag Glu				-	192
Jei	50	Uy 3	ush	Leu	n y	55	uiu	1111	ury	Lys	60	116	116	116	aiu	

	Arg								gtt Val							240
									gcc Ala 90							288
									gaa Glu							336
									acc Thr							384
			gga Gly		-	_	taa *									408
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/al	Ala	Asn	Xaa 20	Asp	Thr	Ala		Lys 25	Val	Gly	Thr	Tyr	G1n 30	Leu	Ala	
le		A1 a 35	Lys	His	His				Phe	Tyr	Val	Ala 45		Pro	Ser	
Ser			Asp	Leu				Thr	Gly	Lys	G1u 60		Пe	Пе	Glu	
ilu 55		Pro	Gly				Thr	Asp	Val	Asn 75		Val	Arg	Ile	A1 a 80	
	Pro	Gly		G1y 85	Val	Trp .	Asn	Pro	A1a 90		Asp	Val	Thr	Pro 95		

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			agt Ser				-						Met	-		384
	-		ttt Phe			-										432
	-	-	ctg Leu	-					_	_	_	_	_	-	•	480
	_		ggc Gly		-	-						-				528
_		-	gag Glu 180		_			_			_		_		-	576
			cag Gln				_	-				_				624
-		-	ctg Leu	_	Āsp		-			-					_	672
			cat His		-				Val		-		-			720
			acc Thr													768
		Val	gga Gly 260					-	_	-	-		-		_	816
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32

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Glu	Phe	Glu 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr		
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-	•		•		gaa Glu 150		_								-		480
	•		-	-	caa G1n	-				-	-				_	·	528
	_			_	gaa Glu	_	_		_				-		-		576
		_	_		ttc Phe		_				-	_					624
-					cca Pro				_				-	-	-	•	672
		-	_		gag Glu 230	-		_			_						720
					ggt Gly												768
					atc Ile	-			•		-	-					816
			-		cag G1n		_	_						_			864
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc		912

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Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu	
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						gcc Ala							-		_	1008
-				-		aag Lys			_	-			-		_	1056
						tac Tyr		_			_	_			_	1104
						tgc Cys 375										1152
						cat His						-	_			1200
	_	_			-	ggc Gly	_	_			_		_	-		1248
			-	-		cac His	-			-			-	_		1296
						ggc Gly		-	_						_	1344
						cgc Arg 455										1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

35

Thr Phe Asn Arg Ser Ser Thr Leu Ile Gln His Gln Arg Ser His Thr 465 470 475 480 ggc gag cgg ccc tac agg tgc gcc gtg tgc ggc aag ggc ttc tgc cgc 1488 Gly Glu Arg Pro Tyr Arg Cys Ala Val Cys Gly Lys Gly Phe Cys Arg 485 490 tcc tcc acg ctt ctg cag cat cac cgg gtc cac agt ggc gag cgg cct 1536 Ser Ser Thr Leu Leu Gln His His Arg Val His Ser Gly Glu Arg Pro 500 505 tac aag tgc gat gac tgc gga aag gcc ttc tcc cag agc tcc gac ctc 1584 Tyr Lys Cys Asp Asp Cys Gly Lys Ala Phe Ser Gln Ser Ser Asp Leu 515 520 525 1623 atc cgc cac cag cgg acc cac gcg gcg ggc cgg cgc tga Ile Arg His Gln Arg Thr His Ala Ala Gly Arg Arg \* 530 535 540 <210> 22 <211> 540 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(540) <223> Xaa = Any Amino Acid <400> 22 Met Glu Arg Glu Ala Leu Pro Trp Gly Leu Glu Pro Gln Asp Val Gln 5 10 Ser Ser Asp Glu Met Arg Ser Pro Glu Gly Asn Leu Arg Gly Asn Met 25 Ser Glu Asn Glu Glu Glu Glu Ile Ser Gln Gln Glu Gly Ser Gly Asp 40 Tyr Glu Val Glu Glu Ile Pro Phe Gly Leu Glu Pro Gln Ser Pro Gly Phe Glu Pro Gln Ser Pro Glu Phe Glu Pro Gln Ser Pro Arg Phe Glu 75 Pro Glu Ser Pro Gly Phe Glu Ser Arg Ser Pro Gly Leu Val Pro Pro 90 Ser Pro Glu Phe Ala Pro Arg Ser Pro Glu Ser Asp Ser Gln Ser Pro

			100					105		•			110		
Glu	Phe	G1u 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr
Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
G1u 145	Ser	Ser	Arg	Tyr	Glu 150	Ser	Gln	Asn	Thr	G1u 155	Leu	Lys	Thr	Gln	Ser 160
Pro	Glu	Phe	Glu	Ala 165	Gln	Ser	Ser	Lys	Phe 170	G1n	Glu	Gly	Ala	Glu 175	Met
Leu	Leu	Asn	Pro 180	Xaa	Glu	Lys	Ser	Pro 185	Leu	Asn	Пe	Ser	Val 190	Gly	Val
His	Pro	Leu 195	Asp	Ser	Phe	Thr	G1n 200	Gly	Phe	Gly	Glu	G1n 205	Pro	Thr	Gly
Asp	Leu 210	Pro	Ile	Gly	Pro	Pro 215	Phe	Glu	Met	Pro	Thr 220	Gly	Ala	Leu	Leu
Ser 225	Thr	Pro	Gln	Phe	G1u 230	Met	Leu	Gln	Asn	Pro 235	Leu	Gly	Leu	Thr	G1y 240
Ala	Leu	Arg	Gly	Pro 245	Gly	Arg	Arg	Gly	G1y 250	Arg	Ala	Arg	Gly	G1y 255	Gln
		-	Pro 260					265					270		_
_		275	Leu				280					285		-	
-	290	-	Glu			295			1		300			,	
305			Gln	_	310			-		315		-	-	-	320
			Lys	325					330					335	
Arg	Thr	His	Ser 340	Gly	Gln	Lys	Pro	Tyr 345	Lys	Cys	Pro	His	Cys 350	Gly	Lys
Ala	Phe	G1y 355	Asp	Ser	Şer	Tyr	Leu 360	Leu	Arg	His	G1n	Arg 365	Thr	His	Ser
His	G1u 370	Arg	Pro	Tyr	Ser	Cys 375 <sub>.</sub>	Thr	Glu	Cys	Gly	Lys 380	Cys	Tyr	Ser	Gln
Asn 385	Ser	Ser	Leu	Arg	Ser 390	His	Gln	Arg	Vạl	His 395	Thr	Gly	Gln	Arg	Pro 400
Phe	Ser	Cys	Gly	I1e 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
Пe	Pro	His	A1a 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	Gly 435	Lys	Arg	Phe	Gly	G1n 440	Ser	Ser	Val	Leu	Ala 445	Пe	His	Ala
Δra	Thr	Hic	رام ا	Dro	Glv	Δra	Thr	Tyr	Sar	Cvs	Pro	Acn	Cvc	Glv	Lve

	450					455					460						
Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	Gln	Arg	Ser	His	Thr 480		
Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg		
			500					505				Gly	510	•			
		515					520					Ser 525	Ser	Asp	Leu		
Ile	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg <sub>.</sub>	Arg 540						
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-	gag		gcg	-	_	-		_		_		cgc Arg					48
												gag Glu					96
_		_		_	-		_					atc Ile 45		-			144
												gtg Val					192
							-					ctg Leu					240
_	-		-		_				-			ttt Phe					288

38

85 90 95 aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cgc · 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly \* 130 135 <210> 24 <211> 143 <212> PRT <213> Homo sapiens <400> 24 Met Glu Pro Ala Leu Arg Ala Val Cys Lys Asp Val Arg Ile Gly Thr 10 Ile Leu Ile Gln Thr Asn Gln Leu Thr Gly Glu Pro Glu Leu His Tyr Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp 40 Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu 55 Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu 75 Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arq Val 85 90 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 120 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly 130 135 140 <210> 25

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145					150					155	5				160	
					He				gtg Val 170							528
				Ser					act Thr					Pro		576
			Glu					Phe	ttc Phe				Ser			624
									gtc Val							672
aat Asn 225	gaa Glu	gac Asp	atc Ile	aaa Lys	ggc Gly 230	tcg Ser	tgg Trp	tcc Ser	agc Ser	aag Lys 235	agg Arg	ggc Gly	ggt Gly	gag Glu	gcc Ala 240	720
									att Ile 250							768
gtg Val	ctc Leu	tgt Cys	ggc Gly 260	ccc Pro	cta Leu	cct Pro	ccc Pro	agc Ser 265	cta Leu	att Ile	gac Asp	cgg Arg	agg Arg 270	gga Gly	ttt Phe	816
						Leu			ccc Pro							864
gcc Ala	tgc Cys 290	aga Arg	gcc Ala	aag Lys	Pro	gat Asp 295	gcc Ala	agc Ser	atg Met	gta Val	gga Gly 300	ggc Gly	cac His	ccc Pro	tga .*	912

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<213> Homo sapiens

<400> 26 Met Leu Ala Gly His Gly Gly Val Phe Ala Leu Thr Leu Leu Leu Ile Leu Thr Thr Gly Leu Phe Phe Val Phe Asp Cys Pro Tyr Leu Ala Arg Lys Leu Thr Leu Ala Ile Pro Ile Ile Ala Ala Ile Leu Phe Phe Phe Val Met Ser Cys Leu Leu Gln Thr Ser Phe Thr Asp Pro Gly Ile 55 Leu Pro Arg Ala Thr Val Cys Glu Ala Ala Ala Leu Glu Lys Gln Ile 75 Asp Asn Thr Gly Ser Ser Thr Tyr Arg Pro Pro Pro Arg Thr Arg Glu Val Leu Ile Asn Gly Gln Met Val Lys Leu Lys Tyr Cys Phe Thr Cys 105 Lys Met Phe Arg Pro Pro Arg Thr Ser His Cys Ser Val Cys Asp Asn 120 Cys Val Glu Arg Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val 135 140 Gly Arg Arg Asn Tyr Arg Phe Phe Tyr Ala Phe Ile Leu Ser Leu Ser 150 Phe Leu Thr Ala Phe Ile Phe Ala Cys Val Val Thr His Leu Thr Leu 165 170 Arg Ala Gln Gly Ser Asn Phe Leu Ser Thr Leu Lys Glu Thr Pro Ala 185 Ser Val Leu Glu Leu Val Ile Cys Phe Phe Ser Ile Trp Ser Ile Leu 200 Gly Leu Ser Gly Phe His Thr Tyr Leu Val Ala Ser Asn Leu Thr Thr 215 Asn Glu Asp Ile Lys Gly Ser Trp Ser Ser Lys Arg Gly Gly Glu Ala 230 235 Ser Val Asn Pro Tyr Ser His Lys Ser Ile Ile Thr Asn Cys Cys Ala 250 Val Leu Cys Gly Pro Leu Pro Pro Ser Leu Ile Asp Arg Arg Gly Phe 265 Val Gln Ser Asp Thr Val Leu Pro Ser Pro Ile Arg Ser Asp Glu Pro 280 Ala Cys Arg Ala Lys Pro Asp Ala Ser Met Val Gly Gly His Pro 295

<210> 27

<211> 795

<212> DNA

<213> Homo sapiens

.PCT/US00/29052

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130 135 140 480 qca cca gtg gaa aaa cct aag cca gaa gat gat ttt cca gat aat tat Ala Pro Val Glu Lys Pro Lys Pro Glu Asp Asp Phe Pro Asp Asn Tyr 145 155 160 150 528 gaa aag ttt atg gag act aaa aaa gca aaa gaa agt gaa gac aag gaa · Glu Lys Phe Met Glu Thr Lys Lys Ala Lys Glu Ser Glu Asp.Lys Glu 165 aac ctt ccc aaa agg aca tct cct ggt ggc ttc aaa ttt act ttc tcc 576 Asn Leu Pro Lys Arg Thr Ser Pro Gly Gly Phe Lys Phe Thr Phe Ser 180 185 190 cac tot god agt got got aat gga aca aac agt aaa tot gta gtg got 624 His Ser Ala Ser Ala Ala Asn Gly Thr Asn Ser Lys Ser Val Val Ala 195 200 205 cag ata cca cca gca act tct aat gga tcc tct tcc aaa acc aca aac 672 Gln Ile Pro Pro Ala Thr Ser Asn Gly Ser Ser Ser Lys Thr Thr Asn 210 215 220 720 ttg cct acg tca gta aca gcc acc aag gga agt ttg gtt ggc tta gtg Leu Pro Thr Ser Val Thr Ala Thr Lys Gly Ser Leu Val Gly Leu Val 235 225 230 768 gat tat cca gat gat gaa gag gaa gat gaa gaa gan tcg tcc ccc Asp Tyr Pro Asp Asp Glu Glu Glu Glu Glu Glu Xaa Ser Ser Pro 245 255 250 795 agg aaa aga cct cgt ctt ggc tca taa Arg Lys Arg Pro Arg Leu Gly Ser \* 260 <210> 28 <211> 264 <212> PRT <213> Homo sapiens <220>

<221> VARIANT <222> (1)...(264)

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<220>

<221> CDS

<213> Homo sapiens

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			-	-		-								cgg Arg		96
														gaa Glu		144
		-				_	-	-			-	-		ctt Leu	_	192
				_	_	•		_		_		_		att Ile	•	240
-	_	-			-				-	-			-	aac Asn 95		288
-			-	_	_						_	_		aaa Lys		336
				_	-					_			-	cta Leu		384
										Lys				tac Tyr		432
-		_	_	Glu	-	-					_			gct Ala		480
cag	ctg	gct	gga	ctg	aca	ttg	t <b>t</b> g	aca	aac	atg	act	gtt	acc	aat	gac	528

														-			
Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp		
	cag Gln		_			-							_			57	'6
	act Thr	-,-				_	_			-	_		_		-	62	?4
	ttg Leu 210		_						_	Gly			-	-		67	2
	gat Asp					Ser		_		-	Thr	tag *				71	1
	<2 <2 <2	210> 211> 212> 212> 213>	236 PRT Homo	s s.a.p	oiens	5											
Met	Gly			Arg 5	Gly	Ala	Gly	Trp	Val 10	Ala	Ala	Gly	Leu	Leu 15	Leu		
	Ala	G1y	A1a 20	_	Tyr	Cys	Пe	Tyr 25		Leu	Thr	Arg	Gly 30		Arg		
Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40	Arg	Ser	Ser	Lys	Ser 45	Ala	Glu	Asp		
Leu	Thr 50	Asp	Gly	Ser	Tyr	Asp 55	Asp	Val	Leu	Asn	A1a 60	Glu	Gln	Leu	Gln		
Lys 65	Leu	Leu	Tyr	Leu	Leu 70	Glu	Ser	Thr	Glu	Asp 75	Pro	Val	Пe	Ile	Glu 80		
Arg	Ala	Leu	Ile	Thr 85	Leu	Gly	Asn	Asn	A1a 90	Ala	Phe	Ser	Val	Asn 95	Gln		
Ala	Ile	Ile	Arg 100	Glu	Leu	Gly	Gly	Ile 105	Pro	Ile	Val	Ala	Asn 110		Ile		
Asn	His	Ser 115	Asn	Gln	Ser	Ile	Lys 120		Lys	Ala ·	Leu	Asn 125		Leu	Asn		
Asn	Leu 130		Val	Asn	Val	Glu 135		Gln	Пe	Lys	Ile 140		Ile.	Tyr	Ile		

Ser 145	Gln	Val	Cys	Glu	Asp 150		Phe	Ser	Gly	Pro 155		Asn	Ser	Ala	Val 160		
	Leu	Ala	Gly	Leu 165		Leu	Leu	Thr	Asn 170	Met		Val	Thr	Asn 175	Asp		
His	Gln	His	Met 180		His	Ser	Tyr	Ile 185		Asp	Leu	Phe	Gln 190	Val	Leu	•	
Leu	Thr	Gly 195		Gly	Asn	Thr	Lys 200	۷a٦ <sub>.</sub>	Gln	Val	Leu	Lys 205	Leu	Leu	Leu		
Asn	Leu 210	Sẹr	Glu	Asn	Pro	A1a 215	Met	Thr	Glu	Gly	Leu 220	Leu	Arg	Ala	Gln		
Va1 225	Asp	Ser	Ser	Phe	Leu 230	Ser	Leu	Met	Thr	A1a 235	Thr						
	<2 <2	212>	31 173 DNA Homo		oi en:	S				•							
	<2	220> 221> 222>	CDS (1)	(1	1737												
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										gag Glu							96
					Leu	Ala				gaa Glu		_	_			1	44
	_		_	_			_	-		ccc Pro		_		_	•	1	92
									-	aac Asn 75				_	_	2	40
cag	gag	tgg	ctg	gcg	qct	ata	aac	gat	gac	tat	act	act	ata	atc	taa	2	38

									•							
Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Val 95	Trp	
	cct Pro															336
	tgg Trp															384
-	ctc Leu 130			_												432
	aca Thr															480
	cag Glņ															528
	tcc Ser															576
	gcc Ala						_		_	_	_			_		624
	gtc Val 210															672
	gca Ala															720
	ttc Phe	-	-			-		-		-						768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	,999	tac	atg	aat	gtg	816

Val	Ser	Val	His 260		Cys	Asn	G1u	His 265	_	Tyr	Gly	Tyr	Met 270		Val		
			Ser		cag Gln		_	-				-				. 864	
					gca Ala			-			-	_	_	•		912	
					ccc Pro 310											960	
					agc Ser											1008	
					tgg Trp											1056	
					atg Met				_	-						1104	
					ggc Gly						_		-		-	1152	
				Val	ggc Gly 390	-			-						•	1200	
			Ala		ggc Gly											1248	
		Phe			aac Asn		Arg					Arg				1296	
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344	

Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440	Trp	Asp	Leu	Пe	Tyr 445	Leu	Gly	Arg	•
												999 Gly				1392
												tat Tyr				1440
												ctg Leu				1488
												cag Gln				1536
												gtg Val 525				1584
Ala.												999 Gly				1632
				Thr					Pro			gat Asp				1680
			Ser		-			Gln			_	cgc Arg	Ser		_	1728
tgg Trp		tga *														1737

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Gly	Pro	Trp	Leu 20	Glu	Ala	Ala	Gly	Va1 25	Ala	Glu	Ser	Pro	Leu 30		Ala
Val	Val	Leu 35	Ala	Ile	Leu	Ala	Arg 40	Asn	Ala	Glu	His	Ser 45		Pro	His
Tyr	Leu 50	Gly	Ala	Leu	Glu	Arg 55	Leu	Asp	Tyr	Pro	Arg 60	Ala	Arg	Met	Ala
Leu 65	Trp	Cys	Ala	Thr	Asp 70	His	Asn	Val	Asp	Asn 75	Thr	Thr	Glu	Met	Leu 80
Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp
Arg	Pro	Glu	Gly 100	Glu	Pro	Arg	Phe	Tyr 105	Pro	Asp	Glu	Glu	G1y 110	Pro	Lys
His	Trp	Thr 115	Lys	Glu	Arg	His	Gln 120	Phe	Leu	Met	Glu	Leu 125	Lys	Gln	Glu
Ala	Leu 130	Thr	Phe	Ala	Arg	Asn 135	Trp	Gly	Ala	Asp	Tyr 140	Ile	Leu	Phe	Ala
Asp 145	Tḥr	Asp	Asn	IJе	Leu 150	Thr	Asn	Asn	Gln	Thr 155	Leu	Arg	Leu	Leu	Met 160
Gly	Gln	Gly	Leu	Pro 165	Val	Val	Ala	Pro	Met 170	Leu	Asp	Ser	Gln	Thr 175	Tyr
Tyr	Ser	Asn	Phe 180	Trp	Cys	Gly	Ile	Thr 185	Pro	Gln	Gly	Tyr	Tyr 190	Arg	Arg
		195				•	200			Gln	•	205		•	
4	210					215				Ala	220				
G1y 225	Ala	Asp	Gln	Leu	Ala 230	Phe	Tyr	Pro	Pro	His 235	Pro	Asn	Tyr	Thr <sub>.</sub>	Trp 240
				245					250	Ala				255	
Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val
		275				-	280			Glu		285			
	290					295		·		Pro	300				
305					310					Ser 315					320
Glu	Val	Phe		Ile 325	Ser	Leu	Ala	Arg	Arg 330	Pro	Asp	Arg	Arg	G1u 335	Arg

Met	Leu	Ala	Ser 340	Leu	Trp	Glu	Met	G1u 345	He	Ser	Gly	Arg	Val 350	. Val	Asp
Ala	Val	Asp 355	Gly	Trp	Met	Leu	Asn 360	Ser	Ser	Ala	Пe	Arg 365	Asn	Leu	Gly
Val	Asp 370	Leu	Leu	Pro	Gly	Tyr 375	G1n	Asp	Pro	Tyr	Ser 380	Gly	Arg	Thr	Leu
Thr 385	Lys	Gly	Glu	Val	Gly 390	Cys	Phe	Leu	Ser	His 395	-	Ser	Ile	Trp	G1u 400
Glu	Val	Val	Ala	Arg 405	Gly	Leu	Ala	Arg	Val 410	Leu	Val	Phe	Glu	Asp 415	Asp
Val	Arg	Phe	G1u 420	Ser	Asn	Phe	Arg	Gly 425	Arg	Leu	Glu	Arg	Leu 430	Met	Glu
Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440	Trp	Asp	Leu	He	Tyr 445	Leu	Gly	Arg
Lys	G1n 450	Va1	Asn	Pro	Glu	Lys 455	Glu	Thr	Ala	Val	G1u 460	Gly	Leu	Pro	Gly
Leu 465	Val	Val	Ala	Gly	Tyr 470	Ser	Tyr	Trp	Thr	Leu 475	Ala	Tyr	Ala	Leu	Arg 480
Leu	Ala	Gly	Ala	Arg 485	Lys	Leu	Leu	Ala	Ser 490	Gln	Pro	Leu	Arg	Arg 495	Met
Leu	Pro	Val	Asp 500	Glu	Phe		Pro	11e 505	Met	Phe	Asp	Gln	His 510	Pro	Asn
Glu	Gln	Tyr 515	Lys	Ala	His	Phe	Trp 520	Pro	Arg	Asp	Leu	Val 525	Ala	Phe	Ser
Ala	G1n 530	Pro	Leu	Leu		A1a 535	Pro	Thr	His	Tyr	Ala 540	Gly	Asp	Ala	Glu
Trp 545	Leu	Ser	Asp	Thr	G1u 550	Thr	Ser	Ser	Pro	Trp 555	•	Asp •	Asp	Ser	G1y 560
Arg	Leu	Ile		Trp 565	Ser	Gly	Ser	Gln	Lys 570	Thr	Leu	Arg	Ser	Pro 575	Ala
Trp	Thr											•			

<210> 33

<211> 1152

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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96		_	gca Ala	-		_	_	He	_					-	-	-	
144			cat His		_			-	-	-		-			-		_
. 192		_	gca Ala	-		-	-	-	-								
240	•	-	cag Gln	-	_	_											
288		-	att Ile 95					-									
336	•		ttg Leu														
384	,		aga Arg					-	-	_	_	_	_	-		•	
432			agc Ser			-				_	-			-			
480		_	cca Pro				_			_						_	
528			atg Met 175	~~		_	•				_	-		Gln			
576		gtc	gca	att	gaa	ggt	aaa	ttt	gaa	gaa	gca	atg	gga	ctt	gtg	tat	itg

Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	Glu 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val	
	-						_	ata Ile			_	_	_	_	_	624
_						-	_	cag Gln	-	-		-	_			672
								caa G1n								720
		-		_	-			tta Leu		-	-			_		768
	_	-		-				ggt Gly 265			_			-		816
								gtt Val								864
	-							gag G1u								912
	-			-		-	-	aca Thr		_		-	-	_		960
								act Thr								1008
							Thr	tgg Trp 345						Ser	_	1056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

1152

380

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 365

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375

<210> 34 <211> 383 <212> PRT

<213> Homo sapiens

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Asn	Phe	Val	Пe	Asp 245	Glu	Asn	Пe	Leu	Lys 250	Glu	Glu	Gly	Ile	G1u 255	Asn	
Phe	Asp	Val	Tyr 260	Ala	He	Lys	Pro	G1y 265	His	Pro	Leu	Gln	Pro 270		Phe	
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	Ala 280	Val	Ser	Lys	Lys	Va1 285	Glu	Ser	Thr	
Gly	A1a 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys	Leu	G1n 300	Leu	Gln	Pro	Lys	
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315	Пe	۷al	Lys	Asp	Ser 320	
Leu	Ser	Asp	Asp	Va1 325	۷a۱	Lys	Ala	Thr	Gln 330	Ala	Пe	Tyr	Leu	Phe 335	Glu	
	Ser		340	·				345			·		350		Ū	
	Gly	355					360			·		365	•		Val	
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn		
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	<b>t</b> gc Cys															96
	aac Asn														-	144

	gtg Val 50	Leu										cag Gln	192
	tac Tyr												240
	ctg Leu										_	-	288
	tac Tyr												336
	ctc Leu	_	-		_	_	_	 -		•	•		384
Gln	aat Asn 130												432
	ggt Gly												480
	ttc Phe									-	_		528
	ctc Leu												576
	gag Glu				Arg								624
	ctc Leu 210			Leu									672

-				agc Ser						_	-			720
-				tgt Cys	-	-				_	_	_	_	768
				cag Gln					_	_	_	-	_	816
				atg Met										864
				aac Asn 295						-	_			912
	-		_	 ccc Pro						-			_	960
				 ctc Leu					_	_				1008
				gac Asp										1056
	 	_		atg Met		-	-		-	_	_	_	-	1104
				ggc G1y 375										1152
_		_		ttc Phe				_	_		_	-		1200

_		_	_			ctc Leu					_					1248
						tgg Trp									-	1296
						ctc Leu										1344
	_	-		-	-	ttc Phe 455	_	tga *							•	1371
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net 1	Gly	АТа	Cys	Leu 5	Gly	Ala	Cys	Ser	Leu 10	Leu	Ser	Cys	Ala	Ser 15	Cys	
_eu	Cys	Gly	Ser 20	Ala	Pro	Cys	Ile	Leu 25	Cys	Ser	Cys	Cys	Pro 30	Ala	Ser	
Arg	Asn	Ser 35	Thr	Val	Ser	Arg	Leu 40	He	Phe	Thr	Phe	Phe 45	Leu	Phe	Leu	
Sly	Va1 50	_	Val	Ser	Ile	Ile 55	. •	Leu	Ser	Pro	Gly 60	. •	Glu	Ser	Gln	
_eu	Tyr	Lys	Leu	Pro	Trp 70	Val	Cys	Glu	Glu	G1y 75	Ala	Gly	Ile	Pro		
	Leu	Gln	Gly	His 85		Asp	Cys	Gly	Ser 90		Leu	Gly	Tyr	Arg 95	80 Ala	
/al	Tyr	Arg	Met 100	Cys	Phe	Ala		Ala 105	Ala	Phe	Phe	Phe	Phe 110		Thr	
.eu	Leu	Met	Leu	Cys	Val	Ser	Ser	Ser	Ara	Asp	Pro	Ara	Ala	Ala	Ile	

		115					120					125			
Gln	Asn 130	Gly	Phe	Trp	Phe	Phe 135	Lys	Phe	Leu	He	Leu 140	Val	G1y	Leu	Thr
Val 145		Ala	Phe	Tyr	Ile 150	Pro	Asp	Gly		Phe 155	Thr	Asn	Ile	Trp	Phe 160
Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	Пe	Leu	Ile	Gln	Leu 175	Val
Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185	Asn	Gln	Arg	Trp	Leu 190	Gly	Lys
Ala	Glu	G1u 195	Cys	Asp	Ser	Arg	A1a 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
Thr	Leu 210	Leu	Phe	Tyr	Leu	Leu 215	Ser	Ile	Ala	Ala	Val 220	Ala	Leu	Met	Phe
Met 225	Tyr	Tyr	Thr	Glu	Pro 230	Ser	Gly	Cys	His	G1u 235	Gly	Lys	Val	Phe	11e 240
			Leu	245		•		Ť	250					255	,
			G1n 260					265					270		
Val	Ile	Thr 275	Leu	Tyr	Thr	Met	Phe 280	Val	Thr	Trp	Ser	A1a 285	Leu	Ser	Ser
	290		Gln	-	-	295					300			·	
305			Val		310					315					320
Ala	Pro	Ser	Ile	Va1 325	Gly	Leu	Пe	Пе	Phe 330	Leu	Leu	Cys	Thr	Leu 335	Phe
He	Ser	Leu	Arg 340	Ser	Ser	Asp	His	Arg 345	Gln	Val	Asn	Ser	Leu 350	Met	Gln
		355	Cys				360					365			
	370		Ala			375					380			•	
385			Ser		390					395					400
Leu	His	Val	Met	Met 405	Thr	Leu	Thr	Asn	Trp 410	Tyr	Lys	Pro	Gly	G1u 415	Thr
Arg	Lys	Met	I1e 420	Ser	Thr	Trp	Thr	A1a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
Ser	Trp	A1a 435	Gly	Leu	Leu		Tyr 440	Leu	Trp	Thr	Leu	Va1 445	Ala	Pro	Leu
Leu	Leu 450	Arg	Asn	Arg		Phe 455	Ser								

61

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Thr Tyr Leu Ala Ser Lys Ala Cys Ile Pro Tyr Leu Lys Lys Ser Lys

	130			135					140					
	Ala			atc Ile					Asn					480
			Cys	gct Ala				-	_			-		528
			-	gca Ala	-	-				_		_	-	576
		Trp		aca Thr										624
-				gaa Glu 215	-	_	-	-		_	-			672
				att Ile										720
				aat Asn										768
				aaa Lys										816
				gaa Glu										864
				aaa Lys 295										912
				gaa G1u										960

63

305	310	315	320
	Val Lys Ala Thr	caa gca atc tat ctg Gln Ala Ile Tyr Leu 330	•
		ttt ctt gat ctg aaa Phe Leu Asp Leu Lys 350	• •
•• • • • • • • • • • • • • • • • • • • •		tct gat cag gca gat Ser Asp Gln Ala Asp 365	
		aaa atg ttt tca ggg Lys Met Phe Ser Gly 380	
		aaa ttg aag att aaa Lys Leu Lys Ilė Lys 395	
	Lys Leu Glu Lys	cta atg aat cag atg Leu Met Asn Gln Met 410	
aga ctg tga Arg Leu *			1257

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<211> 418

<212> PRT

<213> Homo sapiens

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Ile	Leu	Val	Asn 100	Asn	Ala	Ser	Ala	Ile 105	Ser	Leu	Thr	Asn	Thr 110	Leu	Asp
Thr	Pro	Thr 115	Lys	Arg	Leu	Asp	Leu 120	Met	Met	Asn	Val	Asn 125	Thr	Arg	Gly
	130				-	135	Cys			-	140	_	•		•
145					150		Ser			155					160
·			٠	165			Tyr		170		-	·	•	175	
	·		180	•			Glu	185		•	•		190		
		195	·		-		Ala 200					205		·	
	210			-		215	Ser		-		220		•		
225					230		Phe			235					240
				245			Пe		250					255	
	·		260			_	Pro	265					270	·	
		275		•			Ala 280			-	·	285			
	290					295	Glu		-		300				-
305					310		Glu			315			-		320
				325			Ala		330					335	
	•		340				Thr	345			•		350		
		355					G1u 360					365			
	370					375	Phe				380				
385					390		Ser			395					400
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66

		115					120				125				
	-		_		_	_			-	gag Glu			_		432
										gag Glu 155					480
										aaa Lys				Lys	528
_		_	_	-	-			-		tca Ser		_		_	-576
_		_				_	_			gat Asp	-	-		_	624
taa *															627

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<211> 208

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<213> Homo sapiens

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 10
 15

 Ile Tyr Met Gly Lys Asp Lys Tyr Glu Asn Glu Asp Leu Ile Lys His 20
 25
 30

 Gly Trp Pro Glu Asp Ile Trp Phe His Val Asp Lys Leu Ser Ser Ala 35
 40
 45

 His Val Tyr Leu Arg Leu His Lys Gly Glu Asn Ile Glu Asp Ile Pro 50
 55
 60

 Lys Glu Val Leu Met Asp Cys Ala His Leu Val Lys Ala Asn Ser Ile 65
 70
 75
 80

 Gln Gly Cys Lys Met Asn Asn Val Asn Val Val Tyr Thr Pro Trp Ser

				85					90					95			
Asn	Leu	Lys	Lys 100	Thr	Ala	Asp	Met	Asp 105	Val	Gly	Gln	Ile	Gly 110	Phe	His		
Arg	Gln	Lys 115	Asp	Val	Lys	IJе	Val 120	Thr	Val	Glu	Lys	Lys 125	Val	Asn	Glu		
Ile	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	Val	Glu	Arg 140	Phe	Pro	Asp	Leu		
Ala 145	Ala	Glu	Lys	Glu	Cys 150	Arg	Asp	Arg	Glu	Glu 155	Arg	Asn	Glu	Lys	Lys 160		
Ala	Gln	Ile	Gln	G1u 165	Met	Lys	Lys	Arg	G1u 170	Lys	Glu	Glu	Met	Lys 175	Lys		
Lys	Arg	Glu	Met 180	Asp	Glu	Leu	Arg	Ser 185	Tyr	Ser	Ser	Leu	Met 190	Lys	Val		
G1u	Asn	Met 195	Ser	Ser	Asn	Gln	Asp 200	Gly	Asn	Asp	Ser	Asp 205	Glu	Phe	Met	·	
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Met 1	Ser	Gly	Ser	Leu 5	Gly	Arg	Ala	Ala	Ala 10	Ala	Leu	Leu	Arg	Trp 15	Arg		
											gtc					g	96
Leu	Cys	Ala	G1y 20	Gly	Gly	Gly	Leu	Trp 25	Gly	Pro	Val	Val	Arg 30	Thr	Ala		
			_					-		-	nag	_	_		_	14	14
ы	ser	35	rro	ыу	ыју	ыу	40	5er	Ala	Хаа	Xaa	Leu 45	ASP	ΑΙα	Leu		
							-				999	_	_		_	19	}2
Val	Lys	Lys	Asp	Lys	val	val	۷al	Phe	Leu	Lys	Gly	Ihr	Pro	Glu	Gln		

68

50 55 60 ccc cag tgc ggc ttc agc aac gcc gtg gtg cag atc ctg cgg ctg cac 240 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 65 70 75 ggc gtc cgc gat tac gcg gcc tac aac gtg ctg gac gac ccg gag ctc 288 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 85 90 cga caa ggc att aaa gac tat tcc aac tgg ccc acc atc ccg caa gtg 336 Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 100 105 110 tac ctc aat ggc gag ttt gta ggg ggc tgt gac att ctt ctg cag atg 384 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 115 120 125 cac cag aat ggg gac ttg gtg gaa gaa ctg aaa aag ctg ggg atc cac 432 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 130 135 tcc gcc ctt tta gat gaa aag aaa gac caa gac tcc aag tga 474 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys \* 145 150 155. <210> 42 <211> 157 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(157) <223> Xaa = Any Amino Acid <400> 42 Met Ser Gly Ser Leu Gly Arg Ala Ala Ala Ala Leu Leu Arg Trp Arg 10 15 Leu Cys Ala Gly Gly Gly Leu Trp Gly Pro Val Val Arg Thr Ala 25 Gly Ser Ala Pro Gly Gly Gly Ser Ala Xaa Xaa Leu Asp Ala Leu 35 45 40

Val	Lys 50	Lys	Asp	Lys	Val	Va1 55	Val	Phe	Leu	Lys	G1y 60	Thr	Pro	Glu	Gln	
Pro 65	Gln	Cys	Gly	Phe	Ser 70	Asn	Ala	Val	Val	G1n 75	Ile	Leu	Arg	Leu	His 80	
Gly	Val	Arg	Asp	Tyr 85	Ala	Ala	Tyr	Asn	Va7 90	Leu	Asp	Asp	Pro	G1u 95	Leu	
Arg	Gln	Gly	Ile 100	Lys	Asp	Tyr	Ser	Asn 105	Trp	Pro	Thr	Ile	Pro 110	Gln	Val	
Tyr	Leu	Asn 115	Gly	Glu	Phe	Val	Gly 120	Gly	Cys	Asp	Ile	Leu 125	Leu	Gln	Met	
His	Gln 130	Asn	Gly	Asp	Leu	Val 135	Glu	Glu	Leu	Lys	Lys 140	Leu	Gly	Ile	His	
Ser 145	Ala	Leu	Leu	Asp	Glu 150	Lys	Lys	Asp	Gln	Asp 155	Ser	Lys				
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													ggt Gly 30			96
													gca Ala		-	144
													tcg Ser			192
													acc Thr			240

	-	-							_	-			aat Asn	-	-	288
		_						_			-		gat Asp 110		-	336
		-	_	-				_				-	gcc Ala			384
_			-		Ile	-	-	_					att Ile	_	_	432
							_	-					gct Ala			480
-				_	_			-	-				aag Lys		_	528
						-		-	-				cct Pro 190	-		576
	_		_	_	-		-		_	_			atg Met		_	624
						-			-				gac Asp	-		672
													gtt Val			7,20
-						-			-				gga Gly			768

WO 01/29221

PCT/US00/29052

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90

Gln Leu Gln Lys Leu Leu Tyr Leu Leu Glu Ser Thr Glu Asp Pro Val 100 105 110 Ile Ile Glu Arg Ala Leu Ile Thr Leu Gly Asn Asn Ala Ala Phe Ser 120 Val Asn Gln Ala Ile Ile Arg Glu Leu Gly Gly Ile Pro Ile Val Ala 135 Asn Lys Ile Asn His Ser Asn Gln Ser Ile Lys Glu Lys Ala Leu Asn 150 155 Ala Leu Asn Asn Leu Ser Val Asn Val Glu Asn Gln Ile Lys Ile Lys 170 165 175 Ile Tyr Ile Ser Gln Val Cys Glu Asp Val Phe Ser Gly Pro Leu Asn 180 185 190 Ser Ala Val Gln Leu Ala Gly Leu Thr Leu Leu Thr Asn Met Thr Val 200 205 Thr Asn Asp His Gln His Met Leu His Ser Tyr Ile Thr Asp Leu Phe 210 215 220 Gln Val Leu Leu Thr Gly Asn Gly Asn Thr Lys Val Gln Val Leu Lys 230 235 Leu Leu Leu Asn Leu Ser Glu Asn Pro Ala Met Thr Glu Gly Leu Leu 245 250 Arg Ala Gln Val Asp Ser Ser Phe Leu Ser Leu Tyr Asp Ser His Val 260 265 Ala Lys Glu Ile Leu Leu Arg Val Leu Thr Leu Phe Gln Asn Ile Lys 275 280 285 Asn Cys Leu Lys Ile Glu Gly His Leu Ala Val Gln Pro Thr Phe Thr 295 300 Glu Gly Ser Leu Phe Phe Leu Leu His Gly Glu Glu Cys Ala Gln Lys 310 Ile Arg Ala Leu Val Asp His His Asp Ala Glu Val Lys Glu Lys Val 325 330 Val Thr Ile Ile Pro Lys Ile 340 <210> 45 <211> 1335 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1335) <221> misc feature <222> (1)...(1335)

73

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_		-	-	-	-	ttt Phe			-						_	96
-						ttg Leu	-		_		-	-		-	•	144
						tat Tyr 55		-				_		-		192
						gaa Glu			-	-		_			-	240
						acg Thr			-		-	-			-	288
						ttg Leu		-								336
						ccc Pro							_			384
						ttc Phe 135										432
						gct Ala										480
gaa	tat	aag	ССС	cţt	tcg	ggc	att	cgg	tac	atg	tgg	tcg	tac	cat	tta	528

Glu	Tyr	Lys	Pro	Leu 165		Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175		
				Trp							gcg Ala					576
			Gly								aac Asn					624
										Leu	tcc Ser 220					672
											tta Leu					720
											aac Asn					768
											tgc Cys					816
											aac Asn					864
											aca Thr 300					912
				Leu							ttt Phe					960
			Asp					Leu			gtg Val					1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

Phe	Thr	Val	Phe 340		Gly	Leu	Met	Ala 345		Asn	Tyr	Asn	Arg 350		Phe	
	gtg Val		Ala					Leu		_			-			1104
	gcc Ala 370											Leu				1152
	ctg Leu															1200
	Pro															1248
	aaa Lys				-		_	_	-	-	_					1296
	gag Glu															1335
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Leu	Ser	Leu	A1 a 20		Met	Phe	Thr	Phe 25		Phe	Пe	Thr	Thr 30		Leu	
Val	His	Пe		Ile	Ser	Leu	Val		Leu	Gly	Leu	Leu		Val	Cys	

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Πe
G1u 65		Asp	Thr	Glu	Arg 70		Asn	Met	Lys	Cys 75		Leu	Gly	Phe	A1 a
	Val	Ser	Thr	G1y 85		Thr	Ala	Val	Leu 90		Val	Leu	Пe	Phe 95	
Leu	Arg	Lys	Arg 100		Lys	Leu	Thr	Val 105	Glu	Leu	Phe	Gln	Ile 110		Asn
Lys	Ala	Ile 115	Ser	Ser	Ala	Pro	Phe 120			Phe	Gln	Pro 125		Trp	Thr
Phe	Ala 130		Leu	Ile	Phe	Phe 135		۷a٦	Leu	Trp	Val 140		Val	Leu	Leu
Ser 145		Gly	Thr	Ala	Gly 150	Ala	Ala	Gln	Val	Met 155		Gly	Gly	Gln	Val 160
Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	
Пe	Gly	Leu	Ile 180	Trp	Thr	Ser	Glu	Phe 185	Ile	Leu	Ala	Cys	Gln 190		Met
Thr	Ile	Ala 195	Gly	Ala	Val	Xaa	Thr 200		Tyr	Phe	Asn	Arg 205		Lys	Asn
Asp	Pro 210	Pro	Asp	His	Pro	Ile 215	Leu	Ser	Ser	Leu	Ser 220	Пe	Leu	Phe	Phe
Tyr 225	His	Gln	Gly	Thr	Ile 230	Val	Lys	Gly	Ser	Phe 235	Leu	Ile	Ser	Val	Val 240
Arg	Ile	Pro	Arg	Ile 245	Пe	Val	Met	Tyr	Met 250	Gln	Asn	Ala	Leu	Lys 255	
Gln	His	Gly	Ala 260	Leu	Ser	Arg	Tyr	Leu 265	Phe	Arg	Cys	Cys	Tyr 270		
Phe	Trp	Cys 275	Leu	Asp	Lys	Tyr	Leu 280	Leu	His	Leu	Asn	G1n 285	Asn	Ala	Tyr
Thr	Thr 290	Thr	Ala	Ile	Asn	Gly 295	Thr	Asp	Phe	Cys	Thr 300	Ser	Ala	Lys	Asp
Ala 305	Phe	Lys	He	Leu	Ser 310	Lys	Asn	Ser	Ser	His 315	Phe	Thr.	Ser	Пe	Asn 320
Cys	Phe	Gly	Asp	Phe 325	Пe	He	Phe	Leu	Gly 330	Lys	Val	Leu	Val	Va1 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Val	Ala	Phe	Phe 365		Tyr	Leu
Val	Ala 370	His	Ser	Phe	Leu	Ser 375	Val.	Phe	Glu	Thr	Va1 380	Leu	Asp	Ala	Leu
Phe	Leu	Cys	Phe	Ala	Val	Asp	Leu	Glu	Thr	Asn	Asp	Gly	Ser	Ser	Glu

385					390					395					400	
Lys	Pro	Tyr	Phe	Met 405	•	Gln	Glu	Phe	Leu 410	Ser	Phe	Val	Lys	Arg 415	Ser	
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Asn	Glu	G1u 435	Gly	Thr	Glu	Leu	G1n 440	Ala	Ile	Val	Arg					
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					_		-			-	-		tta Leu	-		192
				_		-				-	-		aag Lys			240
								_				-	ctt Leu	-	-	288
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78

100 105 110 gaa cat gca tcc taa 351 Glu His Ala Ser \* 115 <210> 48 <211> 116 <212> PRT <213> Homo sapiens <400> 48 Met Ala Asp Glu Ala Leu Phe Leu Leu Leu His Asn Glu Met Val Ser 10 Gly Val Tyr Lys Ser Ala Glu Gln Gly Glu Val Glu Asn Gly Arg Cys Ile Thr Lys Leu Glu Asn Met Gly Phe Arg Val Gly Gln Gly Leu Ile 40 Glu Arg Phe Thr Lys Asp Thr Ala Arg Phe Lys Asp Glu Leu Asp Ile Met Lys Phe Ile Cys Lys Asp Phe Trp Thr Thr Val Phe Lys Lys Gln 75 Ile Asp Asn Leu Arg Thr Asn His Gln Gly Ile Tyr Val Leu Gln Asp Asn Lys Phe Arg Leu Leu Thr Gln Met Ser Ala Gly Lys Gln Tyr Leu 100 105 110 Glu His Ala Ser 115 <210> 49 <211> 516 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(516) <400> 49 atg aag aaa tgt ctt ttg ccc gtt ttg att acg tgc atg caa aca gcg 48 Met Lys Lys Cys Leu Leu Pro Val Leu Ile Thr Cys Met Gln Thr Ala

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			atg Met						96
	Glu		gaa Glu						144
			gaa Glu 55						192
			gtg Val						240
			gcc Ala						288
			acc Thr						336
			tgt Cys						384
			999 Gly 135						432
			ctt Leu						480
	Gly		tgg Trp	Thr		taa *			516

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Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

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81

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-	-	-				aag Lys					-				•	144
-				_	-	gat Asp 55					-				•	192
		_				gaa Glu					_	_	-	_		240
	-		_	_		aca Thr	_	_	_		-	-			-	288
						cct Pro										336
	-				-	gtt Val		-	_	-	-	-		-		384
-					_	ctg Leu 135					_		-		-	432
		_		_	_	ctg Leu	-	_		_	_	-	_		-	480
						gag G1u										528
						gag G1u										576
						gac Asp			_					_		624

82

		-		cag Gln							_	-	_	-	672
				agc Ser 230									_	_	720
_	-	-	_	tgc Cys		-		-	-		-				768
-			_	cac His	-	-				_	_			-	816
-				gaa G1u	-		-	-			-		_		864
ccg Pro	tga *			)											870

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 Met
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 Leu
 Leu
 Lys
 Leu
 Val
 His
 Gly
 Ser
 Pro
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 Val
 Phe
 Gly
 Glu
 Ils
 Ils</th

83

100 105 110 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro 120 125 Lys Gly Lys Lys Phe Leu Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys 135 140 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly Arg 150 155 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly 170 165 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys 180 185 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 200 205 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 230 235 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 245 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His 280 Pro <210> 53 <211> 1041 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1041) <221> misc feature <222> (1)...(1041) <223> n = A,T,C or G<400> 53 48 Met Pro Arg Val Phe Val Phe Arg Ala Leu Leu Leu Val Leu Ile Phe

15

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PCT/US00/29052

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	_	-		ctc Leu					-	_		-	-	_		1	192
		_	_	cag G1n		_		_	_	-		-	-				240
				cgc Arg 85												Ź	288
_	-	_		gtc Val		-					-					3	336
				cta Leu		-				-	-	-	-		_	3	384
-		_		gtc Val			-	-			_			-		2	132
	_			gcc Ala	_		_	_	-	_		-				2	180
_				ttg Leu 165			-		-	-		_		_	_	Ę	528
-				gca Ala		_		-	-	-			-			ξ	576

			gct Ala									624
		-	gcc Ala 215							_	_	672
			ctg Leu								cac His 240	720
			cag Gln				-					768
			cta Leu									816
			cgc Arg				-				_	864
			aat Asn 295			_					_	912
			agc Ser	-	-			_				960
			gag Glu						His			1008
	Arg		gag Glu		_	taa *						1041

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280

Ser	Asp 290	Glu	Ala	Val	Ihr	Asn 295	Gly	Leu	Arg	Asp	Gly 300	lle	Va1	Phe	Val	
Leu 305	Lys	Cys	Leu	Asp	Phe 310	Ser	Leu	Val	۷a۱	Asn 315	Val	Lys	Lys	Пe	Pro 320	
Phe	Ile	Пe	Leu	Ser 325	Glu	Glu	Phe	Ile	Asp 330	Pro	Lys	Ser	His	Lys 335	Phe	
Val	Leu	Arg	Leu 340	Gln	Ser	Glu	Thr	Ser 345	Val							
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Glu	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Thr	Arg	Ala 45	Asn	His	Asn	
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Met 1	Gly	Thr	Ser	Asp 5	Ser	His	His	Ala	Gly 10	Leu	Ser	Leu	Val	Ser 15	Arg	
							999 Gly									96
						_	gag Glu 40				-			-	_	144
							cat His									192
							gtg Val		-	_	-		-		-	240
							tcc Ser			-					-	288

-		_	-			tat Tyr				_	_					336
						ttg Leu			-	-		-		-		384
	_	_				cct Pro 135		_	_					_	_	432
						atc Ile						_				480
-			_	_	_	atg Met										528
	_				_	gat Asp	_	_	-							576
						gga Gly	-	-	_		-		-	-	_	624
						tct Ser 215										672
						tca Ser					-		-		_	720
						agt Ser	_							_		768
						gtc Val										816

-			_	-		-	-		_		 aag Lys	•	864
-	_		-		-			 			gtc Val	_	912
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<211> 336

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<213> Homo sapiens

<400> 58

115

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 Leu Asp Glu Val Asp Glu Val Asp 20

 Met Ser Asp Leu Ser Pro Glu Glu Glu Glu Glu Trp Arg Val Glu His Ala Arg 35
 40
 45

 Met His Ala Lys His Arg Gly His Solu Ala Met His Ala Glu Met Val 50
 55
 60

 Leu Ile Leu Ile Ala Thr Leu Val Val Ala Gln Leu Leu Leu Leu Val Gln 65
 70
 75
 80

 Trp Lys Gln Arg His Pro Arg Ser Tyr Asn Met Val Thr Leu Phe Gln 90
 95

 Met Trp Val Val Val Pro Leu Tyr Phe Thr Val Lys Leu His Trp Trp Arg 100
 105
 110

 Phe Leu Val Ile Trp Ile Leu Phe Ser Ala Val Thr Ala Phe Val Thr

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Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile
                    150
                                        155
Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu
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                                    170
Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu
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                                185
Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met
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                                                 205
Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly
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                                            220
Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln
                    230
                                        235
Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr
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                                    250
                                                         255
Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp
                                265
Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val
                            280
Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met
                        295
Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro
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Val Ile Ile Gly Val Val Gln Gly Ile Asn Tyr Ile Leu Gly Leu Glu
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1
                 5
                                     10
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	-		ctg Leu													1	.92
	-		cct Pro	-	-			-		-						2	240
		-	gcc Ala	-	_	_		_	_	_	_	_	_			2	288
			tac Tyr 100													3	336
	-		aac Asn	_	_		-			-			-			3	884
ctc Leu	agc Ser 130	tag *														3	193
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		35					40				45				
_	cac His 50	-	_		_	_		_	-	_			-	-	192
	cct Pro		_					_	-		-	-			240
	tcc Ser							-				_			288
	tct Ser	-		-		-	_		_	-					336
-	gag Glu	_			_					-			-	-	384
	gga Gly 130				_			-			_				432
	gga Gly	-		-			_		_					-	480
	ttg Leu														528
	att Ile							_							576
-	agt Ser		-			-	_	_							624
	ttc Phe					-		-	-		-				672

	210		•			215					220						
	Asn					ttt Phe									•	720	
						gca Ala			_						_	768	
						aca Thr	-	-							_	816	
						cta Leu	_	_						-		864	
-		_	-	-		ccc Pro 295		_		_			_		_	912	
						gat Asp										960	
			_		-	acc Thr	-				_			-		1008	
					_	gag Glu								-		1056	
					_	999 Gly	_	-		-		-	_			1104	
						tcc Ser 375										1152	
						gct Ala										1200	

96

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Cys	Glu	Asp 115		Pro	Lys	His	Lys 120		Arg	Pro	Ser	His 125	Ser	Glu	Val
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Leu 145		Leu	Пe	Leu	Thr 150	Pro	Leu	IJе	Lys	Lys 155	Ser	Tyr	Phe	Pro	Lys 160
Ile	Leu	Thr	Phe	Phe 165	Val	Gly	Leu	Ala	Ile 170	G1y	Thr	Leu	Phe	Ser 175	Asr
			180					185				·	Pro 190	-	
Asp	Ser	Tyr 195	Val	Glu	Lys	Ala	Va1 200		Val	Phe	-G1y	G1y 205	Phe	Tyr	Leu
	210					215					220	_	Thr	•	·
225					230					235			Pro		240
				245					250			_	Val	255	•
			260					265					His 270		-
		275					280	·	-	-	•	285	Pro		
	290					295	-				300	_	Thr		
305					310	·				315			Asp	•	320
				325					330			•	Leu	335	
Ser	He	Ala	11e 340	Leu	Cys	Glu	Glu	Phe 345	Pro	His	Glu	Leu-	G1y 350	Asp	Phe
		355					360					365	Leu		
	370				_	375	Ť	Ť		·	380		Phe	·	
385					390					395			Leu		400
				405					410				Glu	415	
Asp	Met	Leu	Arg 420	Glu	Lys	Val	Thr	G1y 425	Arg	Lys	Thr	Asp	Phe 430	Thr	Phe
Phe		I 1e 435	Gln	Asn	Ala	Gly	Met 440	Leu	Thr	Gly	Phe	Thr 445	Ala	Пe	Leu
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												gcg Ala		144
												cct Pro	_	192
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												gtg Val		336
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-	ctc Leu 50	-	-												_	192
-	aaa Lys		-							-				-		240
-	tcc Ser					-	_	_				-	_	_	-	288
-	tcc Ser	_	-				-	-		-					_	336
	aca Thr		•	-			-			-				-		384
-	ctg Leu 130	_		-			_	_			_		_		_	432
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1 Val	Sar	الم أ	Dhe	5 1 au	Gln	د ۵۱	Cvc	Dho	10	Thr	دΙ۵	Πρ	Acn	15 Tyr	Lou	

Val Ser Leu Phe Leu Gln Ala Cys Phe Leu Thr Ala Ile Asn Tyr Leu

Leu	Ser	Arg 35	His	Met	Ala	His	Lys 40	Ser	Glu	Gln	Ile	Leu 45	Lys	Ala	Ala	
Ser	Leu 50	Gln	Val	Pro	Arg	Pro 55	Ser	Pro	Gly	His	His 60	His	Pro	Pro	Ala	
Val 65	Lys	Glu	Met	Lys	G1u 70	Thr	Gln	Thr	Glu	Arg 75	Asp	Ile	Pro	Met	Ser 80	
Asp	Ser	Leu	Tyr	Arg 85	His	Asp	Ser	Asp	Thr 90	Pro	Ser	Asp	Ser	Leu 95	Asp	
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Tyr	Thr	Gln 115	Val	Val	Phe	Ser	Asp 120	Pro	Gly	Glu	Leu	Lys 125	Asn	Asp	Ser	
Pro	Leu 130	Asp	Tyr	Glu	Asn	Ile 135	Lys	Glu	Ile	Thr	Asp 140	Tyr	Val	Asn	Val	
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	cag Gln															144
_	gaa Glu 50						_								_	192

-	_			_	_	gga Gly								_	_	240
-	-	-	_		-	ttc Phe				-		-		-		288
			-			gtg Val								-	-	336
	-	-	-	-	-	atg Met	-		_	-				-	-	384
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Ala	Gln	A1a 35	Arg	Arg	Leu	Gln	Gly 40	Asp	Val	Ala	Gly	Ala 45	Leu	G1u	Asp	
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Asn															•	

Ser	Arg 130													
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	_			-	_	_			 _		aac Asn 45	_		144
											tta Leu			192
											ccc Pro			240
											ttt Phe			288
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Lys	Val	Va1 35		Gly	Arg	Ile	Ile 40		Gly	Tyr	Cys	Arg 45	-	Asp	Trp	
		Ser									cag Gln 60					192
											gtg Val					240
											gcc Ala					288
											cca Pro					336
											tcc Ser					384
											ccc Pro 140					432
											aaa Lys			Met		480
											ctg Leu					528
									Pro		agg Arg					576
	His					Asn					ccc Pro					624
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106

Lys Thr Gln Gly Pro Ser Thr Gly Leu Asp \* 210 215

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Lys Val Val Ser Gly Arg Ile Ile Asn Gly Tyr Cys Arg Gly Asp Trp 35 40 45

Leu Leu Ser Phe Val Tyr Arg Thr Ser Ser Val Gln Leu His Val Ala 50 55 60

Gly Leu Gln Pro Val Leu Leu Gln Asp Arg Val Glu Asn Val Asp 65 70 75 80

Leu Thr Ser Val Val Ser Gly His Leu Asp Tyr Ala Lys Gln Met Asp 85 90 95

Ala Ile Leu Lys Ala Val Gly Ile Arg Thr Lys Pro Gly Trp Asp Glu 100 105 110

Lys Gly Leu Leu Leu Ala Pro Gly Cys Leu Pro Ser Glu Glu Pro Arg 115 120 125

Gln Ala Ala Ala Ala Ser Ser Gly Glu Thr Pro His Gln Val Gly 130 135 140

Gln Thr Gln Gly Pro Ile Ser Gly Asp Thr Ser Lys Leu Ala Met Ser 145 150 155 160

Thr Asp Pro Ser Gln Ala Gln Val Pro Val Gly Leu Asp Gln Ser Glu 165 170 175

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									_	_	_	_		gtc Val	_	144
										-	-	-	-	tac Tyr		192
														cgg Arg		240
														atg Met 95		288
				_					-	-		_		tgt Cys	•	336
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                                25
Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu Ala Asp Trp Val Cys
Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Leu Asp Tyr Glu
                        55
                                             60
Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
65
                    70
                                         75
Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
                85
                                    90
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
            100
                                105
                                                     110
Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
        115
                            120
                                                125
Arg His His Cys Gln Gly Lys Asp Leu Thr Glu Trp Val Asp Gly Cys
    130
                        135
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Asp Phe
145
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Met Leu Cys Phe Leu Arg Gly Met Ala Phe Val Pro Phe Leu Leu Val
                                     10
acc tgg tcg tca gcc gcc ttc att atc tcc tac gtg gtc gcc gtg ctc
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			gag Glu	-						-					-	192
			gca Ala													240
			acc Thr													288
			gga Gly 100													336
	cag Gln	tga *														345
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Thr	Trp	Ser	Ser 20	Ala	Ala	Phe		I1e 25	Ser	Tyr	Val	Val	Ala 30	Val	Leu	
		35	Val				40					45				
	50		Glu			55		_			60					
Phe 65	Leu	Gly	Ala	Ala	Thr 70	Met	Гуr	Thr	Arg	Tyr 75	Lys	He	Val	Gln	Lys 80	

110

Gin Asn Gin Thr Cys Tyr Phe Ser Thr Pro Val Phe Asn Leu Val Ser 85 90 95 
Leu Val Leu Gly Leu Val Gly Cys Phe Gly Met Gly Ile Val Ala Asn 100 105 110 
Phe Gin

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-					_	ctg Leu 135					-		-		-	432
		_		_	-	ctg Leu	_	-		-	_	-	-		-	480
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	-		-	-	-	gag Glu			_			_	-	_	_	576
						gac Asp			-					_		624
						aaa Lys 215							-		-	672
					-	aat Asn						_		_	-	720
				_	-	cca Pro			-			-				768
_	-			-		agt Ser	_				_	_			-	816
						gca Ala										864

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				gca Ala							-		-			960
_	ctg Leu	-	taa *													972
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		100>				_						_				
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_eu	Ala	Arg 35	Arg	Arg	Lys	Lys	11e 40	Leu	Phe	Tyr	Cys	His 45	Phe	Pro	Asp	
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_eu	Val	Asn	Ser	G1n 85	Phe	Thr	Ala	Ala	Va1 90	Phe	Lys	Glu	Thr	Phe 95	Lys	
Ser	Leu	Ser	His 100	Ile	Asp	Pro	Asp	Val 105	Leu	Tyr	Pro	Ser	Leu 110	Asn	Val	
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_ys	Gly 130	Lys	Lys	Phe	Leu	Leu 135	Leu	Ser	Ile	Asn	Arg 140	Tyr	Glu	Arg	Lys	
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113

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Xaa Ser Thr Ala Ala Glu Leu Leu Arg Leu Gly Ala Arg Val Ile Met

15

96

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						gtc Val										24
						cag Gln				_	_				-	28
-	-	-				gca Ala				-	-			-	•	330
						atg Met										384
						ctc Leu 135						-		-		432
-				-	-	tct Ser								_		480
			_	-		agt Ser	-		_				-		_	528
						gct Ala										576
						aat Asn			-							624

		195					200					205				
			aca Thr													672
	Pro		ttc Phe													720
			cag G1n													768
			gga Gly 260													816
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xaa	Ser	Ihr	A1a 20	Ala	Glu	Leu	Leu	Arg 25	Leu	Gly	Ala	Arg	Va1 30	Ile	Met	
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116

Arg Glu Leu Arg Gln Ala Ala Glu Cys Gly Pro Glu Pro Gly Val Ser

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Ser Val Arg Ala Phe Cys Gln Glu Met Leu Gln Glu Glu Pro Arg Leu
Asp Val Leu Ile Asn Asn Ala Gly Ile Phe Gln Cys Pro Tyr Met Lys
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Lys Pro Leu Phe Asn Leu Val Ser Trp Ala Phe Phe Lys Thr Pro Val
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192		cag Gln														
240		gtg Val														
288		ggc G1y · 95														
336		gtg Val														
384		gaa Glu														
432		cca Pro									Asp		Asp	Tyr		
480	_	agc Ser			_	_		-					-			
528		aat Asn 175														
576	gat	cat	tca	gat	ttt	ctg	gac	gct	gat	agt	aca	gga	aat	tcc	ttg	cc

Ser	Leu	Ser	Asn 180	Gly	Thr	Ser	Asp	Ala 185	Asp	Leu	Phe	Asp	Ser 190	His	Asp ·	
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~	atc Ile 210	•			_	•	_	-	•			•	•			672
_	gta Val	-			-				_	-	-				_	720
_	tat Tyr	•	-			-		_	_	_			-		_	768
-	cag Gln	_	-		_	_	-	_	_	-	-	-				816
	tca Ser													_		864
	aat Asn 290			_					-	-						912
	gat Asp	Thr	Glu	Glu		Thr	-		-		Glu					960
	gtt Val				_	-				-		-	-			1008
	cca Pro				-			-		-			_	-		1056
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_	_													tct Ser		1200
														aat Asņ 415		1248
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	-			-			-					-	-	acc Thr	_	1440
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														tta Leu		1536
	Arg	-		_	_	Ala		-	_	_				gaa Glu	_	1584
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120

Arg Gln Arg Ala Glu Ala Arg Glu Arg Lys Glu Lys Glu Ile Gln Trp 530 535 540 gag aca agg tta ttt cat gaa gat gga gaa tgc tgg gtt tat gat gaa 1680 Glu Thr Arg Leu Phe His Glu Asp Gly Glu Cys Trp Val Tyr Asp Glu 545 550 555 cca tta ctg aaa cgt ctt ggt gct gcc aag cat tag 1716 Pro Leu Leu Lys Arg Leu Gly Ala Ala Lys His \* 565 570 <210> 82 <211> 571 <212> PRT <213> Homo sapiens <400> 82 Met Val Glu Ser Ile Lys His Cys Ile Val Leu Leu Gln Ile Ala Lys Asp Gln Ser Asn Ala Glu Lys His Ala Asp Gly Met Ile Ser Thr Ile Asn Pro Val Asp Ala Ile Tyr Gln Pro Ser Pro Leu Glu Pro Val Ile Ser Thr Met Pro Ser Gln Thr Val Leu Pro Pro Glu Pro Val Gln Leu Cys Lys Ser Glu Gln Arg Pro Ser Ser Leu Pro Val Gly Pro Val Leu Ala Thr Leu Gly His His Gln Thr Pro Thr Pro Asn Ser Thr Gly Ser 90 Gly His Ser Pro Pro Ser Ser Ser Leu Thr Ser Pro Ser His Val Asn 105 Leu Ser Pro Asn Thr Val Pro Glu Phe Ser Tyr Ser Ser Glu Asp 120 Glu Phe Tyr Asp Ala Asp Glu Phe His Gln Ser Gly Ser Ser Pro Lys 135 Arg Leu Ile Asp Ser Ser Gly Ser Ala Ser Val Leu Thr His Ser Ser 150 155 Ser Gly Asn Ser Leu Lys Arg Pro Asp Thr Thr Glu Ser Leu Asn Ser 170 Ser Leu Ser Asn Gly Thr Ser Asp Ala Asp Leu Phe Asp Ser His Asp 185 Asp Arg Asp Asp Ala Glu Ala Gly Ser Val Glu Glu His Lys Ser 195 200 205

Val	Ile 210	Met	His	Leu	Leu	Ser 215		Val	Arg	Leu	G1y 220	Met	Asp	Leu	Th
Lys 225		۷a۱	Leu	Pro	Thr 230		Ile	Leu	Glu	Arg 235	Arg	Ser	Leu	Leu	G10 240
Met	Tyr	Ala	Asp	Phe 245		Ala	His	Pro	Asp 250	Leu	Phe	Val	Ser	I 1e 255	Sei
Asp	G1n	Lys	Asp 260	Pro	Lys	Asp	Ąrg	Met 265		Gln	Val	Val	Lys 270	Trp	Туі
Leu	Ser	A1 a 275	Phe	His	Ala	Gly	Arg 280	Lys	Gly	Ser	Val	A1a 285	Lys	Lys	Pro
Tyr	Asn 290	Pro	Пe	Leu	Gly	G1u 295		Phe	Gln	Cys	His 300	Trp	Thr	Leu	Pro
Asn 305	Asp	Thr	Glu	Glu	Asn 310	Thr	Glu	Leu	Val	Ser 315	Glu	Gly	Pro	Val	Pro 320
Trp	Val	Ser	Lys	Asn 325	Ser	Val	Thr	Phe	Va1 330	Ala	Glu	G1n	Val	Ser 335	His
His	Pro	Pro	Ile 340	Ser	Ala	Phe	Tyr	A1a 345	Glu	Cys	Phe	Asn	Lys 350	Lys	Πe
Gln	Phe	Asn 355	Ala	His	Ile	Trp	Thr 360	Lys	Ser	Lys	Phe	Leu 365	Gly	Met	Ser
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Ser	Lys	Thr	Gly 420	Tyr	Ser	Ala	Asn	I1e 425	He	Phe	His	Thr	Lys 430	Pro	Phe
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Tyr 465	Ala	Lys	Tyr	Ala		Gly				Va1 475			•		Lys 480
Lys	Leu	Pro	Ile	Ile 485	Lys	Lys	Lys	Vaì	Arg 490	Lys	Leu	Glu	Asp	G1n 495	Asr
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Arg	Gln 530	Arg	Ala	Glu	Ala	Arg 535	Glu	Arg	Lys	Glu	Lys 540	G1u	Пe	Gln	Trp
G1u 545	Thr	Arg	Leu	Phe	His 550	Glu	Asp	Gly	Glu	Cys 555	Trp	Val	Tyr	Asp	G1u 560

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														ccc Pro		144
														tac Tyr		192
														cgt Arg		240
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							-					_	-	gct Ala	_	384

		Asp				ttc Phe 135						Пe			ttc Phe	4	432
	Pro					tat Tyr										4	480
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Ala		Leu 35		Ser	Ser	Arg			Met	Gly	Phe	A1a 45		Pro	Phe		
Thr	Asn 50	Lys	Arg	Lys	Ala	Tyr 55	Ser	Glu	Arg	Arg			Gly	Tyr	Ser		
1et 55		Glu	Met	Tyr	G1u 70	Val	Val	Ser	Asn	Val 75	60 G1n	Glu	Tyr	Arg	G1u 80		
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124

His Leu Lys Ala Gln Leu Glu Val Gly Phe Pro Pro Val Met Glu Arg 100 105 110 Tyr Thr Ser Ala Val Ser Met Val Lys Pro His Met Val Lys Ala Val 115 120 125 Cys Thr Asp Gly Lys Leu Phe Asn His Leu Glu Thr Ile Trp Arg Phe 135 140 Ser Pro Gly Ile Pro Ala Tyr Pro Arg Thr Cys Thr Val Asp Phe Ser 150 155 Ile Ser Phe Glu Phe Arg Ser Leu Leu His Ser Gln Leu Ala Thr Met Phe Phe Asp Glu Val Val Lys Gln Asn Val Ala Ala Phe Glu Arg Arg 185 Ala Ala Thr Lys Phe Gly Pro Glu Thr Ala Ile Pro Arg Glu Leu Met 200 205 Phe His Glu Val His Gln Thr 210 215 <210> 85 <211> 615 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(615) <400> 85 48 atg ggg ttt ctg acc tcc tgc agc ctc ctc ttg cct cgg gct gcc cag Met Gly Phe Leu Thr Ser Cys Ser Leu Leu Leu Pro Arg Ala Ala Gln 1 5 10 15 atc ttg gcg gct gag gct ggc tta cct tcg agc cgt tcc ttc atg gga 96 Ile Leu Ala Ala Glu Ala Gly Leu Pro Ser Ser Arg Ser Phe Met Gly 20 25 ttt gct gct ccc ttc acc aac aag cga aag gct tac tcg gag cgt aga 144 Phe Ala Ala Pro Phe Thr Asn Lys Arg Lys Ala Tyr Ser Glu Arg Arg 35 40 45 atc atg ggg tac tca atg cag gag atg tat gag gtg gtg tcc aac gtc 192 Ile Met Gly Tyr Ser Met Gln Glu Met Tyr Glu Val Val Ser Asn Val 50 55 60 cag gag tat cgt gag ttt gtg ccc tgg tgt aag aag tct ctg gtg gta 240

Gln Glu Tyr 65	Arg Glu P	Phe Val Pro 70	Trp Cys	Lys Lys 75	Ser Leu	Val Val 80	
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çct gtc atg Pro Val Met				_	_		336
atg gtc aag Met Val Lys 115	Ala Val C						384
act att tgg Thr Ile Trp 130							432
act gtg gac Thr Val Asp 145	Phe Ser I		-	•			480
cag ctg gcc Gln Leu Ala	_	_		_	-		528
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Gln 65	Glu	Tyr	Arg	Glu	Phe 70		Pro	Trp	Cys	Lys 75		Ser	Leu	Val	Va1 80	
Ser	Ser	Arg	Lys	Gly 85	His	Leu	Lys	Ala	G1n 90	Leu	Glu	Val	Gly	Phe 95	Pro	
Pro	Val	Met	Glu 100	Arg	Tyr	Thr	Ser	Ala 105	Val	Ser	Met	Val	Lys 110	Pro	His	
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Thr	Ile 130	Trp	Arg	Phe	Ser	Pro 135	Gly	Ile	Pro	Ala	Tyr 140	Pro	Arg	Thr	Cys	
Thr 145	Val	Asp	Phe	Ser	Ile 150	Ser	Phe	Glu	Phe	Arg 155	Ser	Leu	Leu	His	Ser 160	
Gln	Leu	Ala	Thr	Met 165	Phe	Phe	Asp	Glu	Val 170	Val	Lys	Gln	Asn	Val 175		
Ala	Phe	Glu	Arg 180	Arg	Ala	Ala	Thr	Lys 185	Phe	Gly	Pro	Glu	Thr 190	Ala	Ile	
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gcc	acc	ctg	aag	acc	atc	cgg	aac	ggc	gtt	cat	aag	ata	gac	acg	tac	144

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														tat Tyr			240
														cat His 95			288
														gac Asp			336
														gaa Glu			384
														cta Leu			432
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Ala	Thr	Leu 35	Lys	Thr	Пe	Arg	Asn 40	Gly	Val	His	Lys	Ile 45	Asp	Thr	Tyr	
	50					55					60				Gln	
65					70		Lys			75					80	
Pro	Ser	Pro	Pro	Asn 85	Gly	Cys	Gly	Ser	Pro 90	Leu	Phe	Gly	Val	His 95	Leu	
			100					105		_			110	·	Arg	
		115					Ser 120					125				
	130					135	Cys				140				_	
145					150		Cys			155					160	
Asp	Ser	Val	Ile	His 165	Leu	Gly	Cys	Lys	Pro 170	Tyr	Leu	Asp	Ser	Gln 175	Arg	
Ala	Ala	Cys	Arg 180	Cys	His	Tyr	Glu	G1u 185	Lys	Thr	Asp	Leu				
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gtg	atc Ile	cag G1n	gtg Val 20	ttc	cag Gln	cag Gln	ctg Leu	ggc Gly 25	tgt	gcg Ala	gtg Val	att Ile	gac Asp 30	gtg	gac Asp	96

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					act Thr 55											192
	_	-	-		gac Asp	-				-		_		~ ~	;	240
	_				acc Thr					-	_		_	-	4	288
					ttc Phe					_				_	;	336
-			_	-	gag Glu		-	-	_		_		_	•	(	384
					tgc Cys 135										2	432
					aac Asn			-	Ala		-	_			2	480
gcc Ala		-		-	gac Asp	_	_	-	_	-	-		-		ξ	528
					agt Ser										5	576
cac His					Ser	_			_	_	_				6	524

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Val	Met	A1 a 35	Arg	His	Val	Val	Gln 40	Pro	Gly	Tyr	Pro	Ala 45		Arg	Arg		
Ile	Va1 50	Glu	Val	Phe	G1y	Thr 55	Glu	Val	Leu	Leu	G1u 60	Asn	Gly	Asp	Ile		
Asn 65	Arg	Lys	Val	Leu	G1 <i>y</i> 70	Asp	Leu	Пe	Phe	Asn 75	G1n	Pro	Asp	Arg	Arg 80		
Gln	Leu	Leu	Asn	A1a 85	Ile	Thr	His	Pro	G1u 90	Ile	Arg	Lys	Glu	Met 95	Met		•
Lys	Glu	Thr	Phe 100	Lys	Tyr	Phe	Leu	Arg 105	Gly	Tyr	Arg	Tyr	Val 110	Ile	Leu		
Asp	Ile	Pro 115	Leu	Leu	Phe	Glu	Thr 120	Lys	Lys	Leu	Leu	Lys 125	Tyr	Met	Lys		
His	Thr 130	Val	Val	Val	Tyr	Cys 135	Asp	Arg	Asp	Thr	Gln 140	Leu	Ala	Arg	Leu		
Met 145	Arg	Arg	Asn	Ser	Leu 150	Asn	Arg	Lys	Asp	Ala 155	Glu	Ala	Arg	Пе	Asn 160		
				165		Asp			170					175			
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	•	195					200		-			205	_		•		
/al	Leu 210	Thr	Gly	Leu		Ala 215	Ile	Ala	Ser	Leu	Leu 220	Tyr	Leu	Leu	Thr		

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ccc gag cgc tgg gga cct ggc cgc ttt gac tac tgg ggc aac tcc cac
                                                                       96
Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
             20
                                 25
                                                      30
cag atc atg cac ctg ctg agc gtg ggc tcc atc ctg cag ctg cac gcc
                                                                      144
Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
         35
                             40
                                                  45
ggc gtc gtg ccc gac ctg ctc tgg gct gcc cac cac gcc tgt ccc cgg
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Gly Val Val Pro Asp Leu Leu Trp Ala Ala His His Ala Cys Pro Arg
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gac tga
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Asp *
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agg cac agc cta ttg tct cct ttg ctc agt gtg aca tca ttc aga cgc
                                                                       96
Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr Ser Phe Arg Arg
             20
                                 25
                                                      30
ttc tac aga ggt gac agc cca aca gat tcc caa aag gac atg att gaa
                                                                      144
Phe Tyr Arg Gly Asp Ser Pro Thr Asp Ser Gln Lys Asp Met Ile Glu
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atc cct ttg cct cca tgg cag gag aga act gat gaa tcc ata gaa acc
                                                                      192
Ile Pro Leu Pro Pro Trp Gln Glu Arg Thr Asp Glu Ser Ile Glu Thr
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                         55
                                             60
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Lys Arg Ala Arg Leu Leu Tyr Glu Ser Arg Lys Arg Gly Met Leu Glu
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	gaa Glu															336
	gac Asp							Ala		-	-		Pro	_		384
-	ata Ile 130		-		-	-	_	_	_	_	•	-		•		432
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	gaa Glu	_		-	-											498
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				65					90					95		
												att Ile				336
									_		-	gct Ala 125			•	384
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Glu	Ile 50		Leu	Pro	Pro	Trp 55		Glu	Arg	Thr	Asp 60	Glu	Ser	Пе	Glu	
Thr 65		Arg	Ala	Arg	Leu 70		Tyr	Glu	Ser	Arg 75		Arg	Gly	Met	Leu 80	
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						aca Thr					-				240
_						cat His		_			-	-		-	288
						ggc Gly									336

			100					105					110			
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G1y	Gly	Ala	•		Leu	Gly	Leu	Glu 105		Ala	Ile	Ile	Gly 110		Ile	
			Tyr 100	Tyr		Gly Val		105	Gly				110	Pro		
Leu	Leu	Cys 115	Tyr 100 Ile	Tyr Leu	Val		Ala 120	105 Ser	Gly Asn	Ile	Tyr ,	Ser 125	110 Ala	Pro Met	Leu	

138

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		100				105			110		
		Gln		tac Tyr							384
				acc Thr 135				Ser			432
•			His	aac Asn							480
				gag Glu							528
				cat His							576
				gcc Ala							624
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				atg Met							720
				tcg Ser							768
				ttg Leu	Пe						816
				gct Ala							864

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									cag G1n 300					912
									atc Ile					960
									gag Glu				_	1008
									cct Pro					1056
									gga Gly					1104
									cgc Arg 380					1152
								_	gag Glu			_		1200
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Glu		-		Glu				-	ttc Phe	-			_	1344
									ttt Phe					1392

141

450 455 460 ccc ctc acc att tca gga aag atc cag aaa ttc aaa ctt cga gag cag 1440 Pro Leu Thr Ile Ser Gly Lys Ile Gln Lys Phe Lys Leu Arg Glu Gln 465 470 475 480 atg gaa cga cat cta aat ctg tga 1464 Met Glu Arg His Leu Asn Leu \* 485 <210> 100 <211> 487 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(487) <223> Xaa = Any Amino Acid <400> 100 Met Trp Gly Pro Asn Ser Tyr Ala Trp Val Leu Met Gln Leu Ala Thr 5 10 15 Ala Gln Ala Gly Ile Ile Leu Val Ser Val Asn Pro Ala Tyr Gln Ala 25 Met Glu Leu Glu Tyr Val Leu Lys Lys Val Gly Cys Lys Ala Leu Val Phe Pro Lys Gln Phe Lys Thr Gln Gln Tyr Tyr Asn Val Leu Lys Gln 55 60 Ile Cys Pro Glu Val Glu Asn Ala Gln Pro Gly Ala Leu Lys Ser Gln 65 70 75 Arg Leu Pro Asp Leu Thr Thr Val Ile Ser Val Asp Ala Pro Leu Pro 90 Gly Thr Leu Leu Leu Asp Glu Val Val Ala Ala Gly Ser Thr Arg Gln 105 His Leu Asp Gln Leu Gln Tyr Asn Gln Gln Phe Leu Ser Cys His Asp 115 120 Pro Ile Asn Ile Gln Phe Thr Ser Gly Thr Thr Gly Ser Pro Lys Gly 135 140 Ala Thr Leu Ser His Tyr Asn Ile Val Asn Asn Ser Asn Ile Leu Gly 150 155 Glu Arg Leu Lys Leu His Glu Lys Thr Pro Glu Gln Leu Arg Met Ile 165 170 175

142

Leu	Pro	Asn	Pro 180	Leu	Tyr	His	Cys	Leu 185	Gly	Ser	Val	Ala	Gly 190	Thr	Met
Met	Cys	Leu 195	Met	Tyr	Gly	Ala	Thr 200	Leu	Ile	Leu	Ala	Ser 205	Pro	Ile	Phe
	210	-			Leu	215				_	220	_	•		
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Phe	Ser	Ser	Tyr	Asp 245	Ile	Ser	Thr	Met	Cys 250	Gly	Gly	Val	Ile	A1 a 255	Gly
			260		Glu			265					270		
Met	Lys	Asp 275	Leu	Val	Val	Ala	Tyr 280	Gly	Thr	Thr	Glu	Asn 285	Ser	Pro	Val
	290				Pro	295	·				300	-			
305	·	Ū			Pro 310					315					320
	-			325	Lys				330	-			•	335	
Gly	Tyr	Cys	Val 340	Met	Leu	Gly	Tyr	Trp 345	Gly	Glu	Pro	Gln	Lys 350	Thr	Glu
Glu	Ala	Va1 355	Asp	Gln	Asp	Lys	Trp 360	Tyr	Trp	Thr	Gly	Asp 365	Val	Ala	Thr
	370			-	Phe	375	•			•	380		•	·	
I1e 385	Ile	Arg	Gly	Gly	G1u 390	Asn	He	Tyr	Pro	A1 a 395	Glu	Leu	Glu	Asp	Phe 400
Phe	His	Thr	His	Pro 405	Lys	Xaa	Gln	Glu	Val 410	Gln	Val	Val	Gly	Val 415	Lys
Asp	Asp	Arg	Met 420	Gly	Glu	Glu	He	Cys 425	Ala	Cys	He	Arg	Leu 430	Lys	Asp
Gly		G1u 435		Thr	Val	Glu			Lys	Ala		Cys 445	Lys	Gly	Lys
Ile	Ser 450	His	Phe	Lys	Пe	Pro 455	Lys	Tyr	Пe	Val	Phe 460	Val	Thr	Asn	Tyr
Pro 465	Leu	Thr	Ile	Ser	Gly 470	Lys	Ile	Gln	Lys	Phe 475	Lys	Leu	Arg	Glu	G1n 480
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				-				_	atc Ile	•						144
		-	-	_		-	-		gat Asp							192
									gta Val							240
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Ala	Ser	Leu	I1e 20	Val	Ala	Arg	Gln	G1y 25	Met	Gly	Asp	Met	A1a 30	Val	Ser	
Asn	Ser	Ile 35	Gly	Ser	Asn	Val	Phe 40	Asp	Ile	Leu	Ile	G1y 45	Leu	Gly	Leu	
Pro	Trp 50	Ala	Leu	Gln	Thr	Leu 55	Ala	Val	Asp	Tyr	Gly 60	Ser	Tyr	Ile	Arg	
Leu 65	Asn	Ser	Arg	Gly	Leu 70	Ile	Tyr	Ser	Val	G1y 75	Leu	Leu	Leu	Ala	Ser 80	•
Val	Phe	Val	Thr	Va1 85	Phe	Gly	Val	His	Leu 90	Asn	Lys	Trp	Gln	Leu 95	Asp	
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qac	agc	ctc	ttc	atc	tat	gac	tac	aqt	act	qca	gaa	aaq	aaq	tca	caa	144
						Åsp										
						gcg		_	_	_		_				192
Glu	Asn 50	Lys	Gly	Glu	Asp	A1a 55	Pro	Leu	Asp	Gln	Gly 60	Ser	Gly	Ala	Ile	

_					tcc Ser 70	_			-			_			-	240
_	_	-	_	•	att Ile			_				~ ~		-	_	288
-	_				gca Ala			_		-					-	336
					ttg Leu											384
					cca Pro											432
-		-	-		gat Asp 150		_		-		-	_	-			480
					gac Asp		-			-	-		_			528
					tcc Ser											576
					cca Pro											624
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	-	-		-	gcc Ala 230	-	_	_		_		-		_	-	720

	-	_		-						ttc Phe			_			768
_				-	-	_				gtg Val	_				_	816
										agg Arg						864
_					-		-			gag Glu				-		912
		-	-	_	-				_	gtg Val 315						960
	-	_		_		-			-	acc Thr			-		_	1008
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	-	-	-		-	-			-	gcc Ala	_		-			1104
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Gln	His 290	Gln	Val	Trp	Asp	Val 295	Ala	Phe	Glu	Glu	Thr 300	Gln	Gly	Leu	Trp	
Va1 305	Leu	Gln	Asp	Cys	Gln 310	Glu	Ala	Pro	Leu	Val 315	Leu	Tyr	Arg	Pro	Val 320	
	Asp	Gln	Trp	Gln 325		Val	Pro	Glu	Ser 330	Thr	Val	Leu	Lys	Lys 335		
Ser	Gly	Val	Leu 340		Gly	Asn	Trp	Ala 345		Leu	Glu	Gly	Ser 350		Gly	
Ala	Asp	A1a 355		Phe	Ser	Ser	Leu 360		Lys	Ala	Thr	Phe 365	Asp	Asn	Val	
Thr	Ser 370		Leu	Lys	Lys	Lys 375	Glu	Glu	Arg	Leu	G1n 380	Gln	Gln	Leu	Glu	
Lys 385	Lys	Gln	Arg	Arg	Arg 390	Ser	Pro	Pro	Pro	G1y 395	Pro	Asp	Gly	His	Ala 400	
Lys	Lys	Met	Arg	Pro 405	Gly	Glu	Ala	Thr	Leu 410	Ser	Cys					
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	ggc Gly			-												144
	ctg Leu 50	-	_				-	-	-		_	_	_	_	_	192
	020	aca	att	aca	act	ata	ana	gaa	aat	ממר	aga	atc	aca	tat	ata	24(

149

G]n 65	Glu	Ala	Ile	Ala	A1a 70	Val	Gly	Glu	Gly	Gly 75	Arg	Ile	Ala	Cys	Va1 80		
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	_					-		-		-	ttt Phe	-	_		gga Gly	;	336
						-					ttg Leu	_			-	Š	384
_		-	-		_		-		-		gca Ala 140	-				4	432
	_		-	_		•			_	-	acc Thr	-	_		_	4	480
_			_		_	_	_			-	atc Ile	_	-		-	;	528
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Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp
Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
Gln Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
                                    90
Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
            100
                                105
Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
                            120
Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
                        135
Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
                    150
                                        155
Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
                165
                                    170
Ala Ala Glu Leu Leu Gly Val Lys Met Cys Thr Phe Val Pro Arg His
                                185
Thr Arg Asn Leu Ala Asn Glu Phe Arg Cys Tyr Val Asn Tyr Asp Ser
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Gly Leu Asp Cys Gly Ile
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                 5
                                     10
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			tgc Cys			cac His	tag *									264
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Trp	Cys	G1 <i>y</i> 35	Glu	Cys	Thr	Ser	Trp 40	Ser	Gly	Val	Trp	Thr 45	Cys	Asp	Asp	
Leu	Leu 50	Thr	Lys	Cys	Ala	A1a 55		Cys	Lys	Asn	Cys 60		Pro	Val	Ser	
Thr 55		Lys	Gly	Ala	Thr 70	Lys	Tyr	Arg	Cys	Arg 75		Phe	Leu	Pro	G1u 80	
	Cys	Gly	Cys	Lys 85		His				, 0						
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			agt ttc cta cat Ser Phe Leu His 30	
			ttt gca aaa gat Phe Ala Lys Asp 45	
		Tyr Asp Ala L	aaa aac gtc gtt _ys Asn Val Val 60	
		-	gaa gga aat ata Glu Gly Asn Ile 75	•
			gtg gat acc aga /al Asp Thr Arg	
Pro Ser Val	=		cag gtt tac cca Gln Val Tyr Pro 110	
	tat act gaa gac Tyr Thr Glu Asp		otg att agt tag Val Ile Ser * 125	378

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Val	Glu	Ser	Ile 20	Cys	Ser	Asn	Asn	Phe 25	Asp	Ser	Phe	Leu	His 30	Glu	Thr		
His	Glu	Asn 35		Tyr	G1y	Lys	Gly 40	Пe	Tyr	Phe	Ala	Lys 45		Ala	Ile		
Tyr	Ser 50		Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60		Val	Met	Phe		
Va1 65	Ala	Gln	Val	Leu	Va1 70	Gly	Lys	Phe	Thr	G1u 75	Gly	Asn	Ile	Thr	Tyr 80		
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	Val	Asp	Thr	Arg	Ser 95	Asn		
Pro	Ser	Val	Phe 100	Val	Ile	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110		Tyr		
Val	Пe	Glu 115	Tyr	Thr	Glu	Asp	Lys 120	Ala	Cys	Val	Пe	Ser 125					
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											aga Arg					1	.44
											gcc Ala 60				-	1	.92

		_			-						ttt Phe		_			Ź	240
-			-								aaa Lys	-				2	288
											gag Glu					(	336
_	_				-	-			-	_	tca Ser		_			3	384
-	-	-		_							tca Ser 140			-		4	132
		_					_			-	tca Ser		-			4	180
	_		_	-	-	-	-		-		cta Leu	-	-		_	Ę	528
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		-	-	-		_	-		_		aaa Lys					6	524
_				_	-			_	_		ggt Gly 220				-	6	572
				Leu							tgg Trp					7	'20

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			_	-	-	tca Ser		-		_	-	-		-	•	816
		-	_	-		gaa G1u	-			-	•	-	-	•		864
_		_			-	tat Tyr 295							_	-		912
_		-		_		gag Glu		_		_			_		-	960
-	_	-			-	gct Ala	_		-		-			_		1008
-			-	-		tct Ser			_	_			_		_	1056
	-			-	-	tgt Cys	-	_					-			1104
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		aag Lys	-									-			-	1296
		cag Gln 435							-	-						1344
		aaa Lys							-						-	1392
	-	gta Val	-	_		-	_			-	-		-		_	1440
		ccc Pro	-	_			_				-				_	1488
		att Ile			-	-		-	-	-						1536
		tct Ser 515									_	-				1584
-		gtt Val	-		-			_	-		_	-	-	_	-	1632
		tct Ser														1680
		aaa Lys									_	-				1728
		gga Gly					Lys									1776

	-			aac Asn	-				-				1824
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Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	He	Leu	Glu	Val	Leu 175	Gln
Ser	Asn	IÌе	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu
Lys	Ala	Leu 195	Ala	Cys	Ile	Pro	Va1 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Ile	Asn	He	Ser
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys	Glu	G1u 240
Phe	Phe	His	Trp	Va1 245	Asn	Asn	Val	Leu	Cys 250		Lys	Cys	Gly	G1y 255	Gln
			260	Asp				265			·	,	270		-
·	-	275	•	Glu			280					285	-		
	290	_		Pro	_	295					300				
Arg 305	Cys	Gly	Arg	Cys	Gly 310	Glu	Trp	Ala	Asn	Cys 315	Phe	Thr	Leu	Cys	Cys 320
_				Phe 325				-	330	·	·	_		335	
	•		340	Val	-			345				·	350		-
Asp	Ala	Cys 355	Glu	Asp	Val	Cys	Asp 360	Lys	Pro	Leu	Leu-	Tyr 365	Glu	Ile	Gly
·	370	-	-	Leu		375					380	_	·		
Va1 385	Asp	Val	Thr	Trp	Arg 390	Tyr	Ser	Cys	Lys	His 395	Glu	Głu	Val	Пe	Ala 400
Arg	Arg	Thr	Lys	Va1 405	Lys	Glu	Ala	Leu	Leu 410	Arg	Asp	Thr	Ile	Asn 415	Gly
Leu	Asn	-		Arg						Glu	Asn	_	Arg 430	Lys	Glu
Leu	Leu	G1n 435	Arg	Ile	Ile	Val	G1u 440	Leu	Val	Glu	Phe	11e 445	Ser	Pro	Lys
Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	He	Ser 460	Gly	Ser	Val	Ala
Trp 465	Arg	Val	Ala	Arg	G1y 470	Glu	Met	Gly	Leu	G1n 475	Arg	Lys	Glu	Thr	Leu 480
Phe	Ile	Pro	Cys	G1u 485	Asn	Glu	Lys	Ile	Ser 490	Lys	Gln	Leu	Ḥis	Leu 495	Cys
Tyr	Asn	Ile	Val	Lys	Asp	Arg	Tyr	Val	Arg	Val	Ser	Asn	Asn	Asn	Gln

Thr	Ile	Ser 515		Trp	Glu	Asn	G1y 520		Trp	Lys	Met	G1u 525	Ser	Пe	Phe	
Arg	Lys 530			Thr	Asp	Trp 535			Val	Tyr	Leu 540		Arg	Lys	Glu	
G1y 545		Ser	Phe	Ala	Tyr 550	Ile	Ser	Trp	Lys	Phe 555		Cys	Gly	Ser	Val 560	
Gly	Leu	Lys	Val	Asp 565	Ser	Ile	Ser	IJе	Arg 570	Thr	Ser	Ser	Gln	Thr 57.5	Phe	
Gln	Thr	Gly	Thr 580	Val	Glu	Trp	Lys	Leu 585	Arg	Ser	Asp	Thr	Ala 590	Gln	Val	
Glu	Leu	Thr 595	Gly	Asp	Asn	Ser	Leu 600	His	Ser	Tyr	Ala	Asp 605	Phe	Ser	Gly	
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Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
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Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
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Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
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Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
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Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
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				gaa Glu 55									192
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				aag Lys							_		288
				gag Glu									336
				ggc Gly			_	_	_			_	384
				tca Ser 135									432
				agt Ser									480
				tcc Ser	-						-	_	528
				ctc Leu									576

			Lys		agg Arg												624
					cgc Arg								_				672
					cga Arg 230												720
					gtc Val												768
					tgc Cys												816
					999 Gly	_				-	-	-	_		•	i	864
ctc Leu	ctc Leu 290	tgt Cys	tct Ser	ccg Pro	cag Gln	cct Pro 295	gat Asp	ggt Gly	aag Lys	gtg Val	gtc Val 300	tac Tyr	acc Thr	tcc Ser	ctg Leu	9	912
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۷alِ	Gly	A1 a 35	Leu	Pro	Arg	Gly	Pro 40	Arg	Gln	Asn	Ser	Arg 45	Leu	Gly	Leu
Pro	Leu 50	Leu	Leu	Met	Pro	G1u 55	Glu	Ala	Arg,	Leu	Leu 60	Ala	Glu	Ile	Gly
A1a 65	Val	Thr	Leu	Val	Ser 70	Ala	Pro	Arg	Pro	Asp 75	Ser	Arg	His	His	Ser 80
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		115					120		Ala	-	-	125	•		
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				165					Gly 170					175	
			180					185	Gln				190		
		195					200		Trp	-		205		_	•
	210					215			Glu		220	-			-
225					230				Leu	235				•	240
				245					Asp 250			•		255	
			260					265	Glu				270		
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cac ato His Ile 145				-								_	-	-	480
atc tco Ile Sen							_					-			528
cga acc Arg Thi	_					-						_			576
ttt gtg Phe Val	-	Phe							-		-	_	-	-	624
gat gcc Asp Ala 210	a Asn		-				_	-						_	672
gct gcc Ala Ala 225		-			-	-					-		_		720
ttg act Leu Thr									-					-	768
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gat gag Asp Glu	-	tga *													828
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Thr Arg Lys Asn Ser Pro Leu His Tyr Tyr Gln Arg Leu Glu Ile Val
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Glu Ala Ala Ile Arg Thr Leu Phe Ser Val Thr Gly Ile Leu Ala Glu
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Gln Phe Val Pro Asp Gly Pro His Leu His Leu Tyr His Glu Asn His
Trp Ile Lys Leu Met Asn Trp Gln His Ser Thr Met Tyr Leu Phe Phe
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                85
Ala Val Ser Gly Ile Val Asp Met Leu Thr Tyr Leu Val Ser His Val
                                105
Pro Leu Gly Val Asp Arg Leu Val Met Ala Val Ala Val Phe Met Glu
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Gly Phe Leu Phe Tyr Tyr His Val His Asn Arg Pro Pro Leu Asp Gln
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His Ile His Ser Leu Leu Leu Tyr Ala Leu Phe Gly Gly Cys Val Ser
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Ile Ser Leu Glu Val Ile Phe Arg Asp His Ile Val Leu Glu Leu Phe
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Arg Thr Ser Leu Ile Ile Leu Gln Gly Thr Trp Phe Trp Gln Ile Gly
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Phe Val Leu Phe Pro Pro Phe Gly Thr Pro Glu Trp Asp Gln Lys Asp
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Asp Ala Asn Leu Met Phe Ile Thr Met Cys Phe Cys Trp His Tyr Leu
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Ala Ala Leu Ser Ile Val Ala Val Asn Tyr Ser Leu Val Tyr Cys Leu
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Leu Thr Arg Met Lys Arg His Gly Arg Gly Glu Ile Ile Gly Ile Gln
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_					ttc Phe	_			_	-		-		-		384
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169

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	_							gcc Ala	-						624
			-				-	gaa Glu					-		672
_	_			_				atg Met			_				720
			•			•		tat Tyr					_		768
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taa *															867
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												ccc Pro 125		-	_		384
-	-					_				-	_	tcc Ser		_		•	432
												gat Asp					480
		-					-	_		-		ttc Phe					528
		_	-	-						-	-	ctg Leu		-	•	;	576

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ctc cgt g Leu Arg G 225		_		_	_	_	-				<b>720</b>
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ctg act o Leu Thr L											816
ggc aaa g Gly Lys G		 	r Tyr	-	_				_	•	864
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tac ccc c Tyr Pro L 305											960
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gtg aaa c Val Lys H			_		-	-			-	_	1104

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His	Phe 290	Gln	His	Ile	Gln	Val 295	Cys	Thr	Pro	Trp	Leu 300	Glu	Ala	Glu	Asp		
Tyr 305	Pro	Leu	Leu	Leu	Gly 310	Ser	Ala	Asp	Leu	Gly 315	Val	Cys	Leu	His	Thr 320		
Ser	Ser	Ser	Gly	Leu 325	Asp	Leu	Pro	Met	Lys 330	Val	۷a٦	Asp	Met	Phe 335	Gly		
Cys	Cys	Leu	Pro 340	Val	Cys	Ala	Val	Asn 345	Phe	Lys	Cys	Leu	His 350	Glu	Leu		
	Lys	355					360	,			·	365					
Ala	Ala 370	G1n	Leu	Gln	Met	Leu 375	Phe	Ser	Asn	Phe	Pro 380	Asp	Leu	Arg	Ala	•	
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177

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Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45	Gln	His	His
Arg	Thr 50	Val	His	Gl'n	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	Val
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Asn	Gly	Leu	Pro	Va1 85	He	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	Glu 95	Arg
Cys	Gln	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
Arg	Gln	Leu 115	Gln	Glu	Glu	Asp	Arg 120	Gly	Ile	Asp	Arg	Val 125	Ala	He	Tyr
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145					150					Asp 155					160
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	·		180					185		Tyr			190	-	
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,	210	-				215				Lys	220	_			
225					230	_				Va1 235			-	_	240
				245			·		250	Ala	·			255	·
			260	·				265		Thr			270		
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	290					295	·			Tyr	300				
305					310					G1u 315			Asn	GIn	Leu 320
Lys	Asp	Ala	He	A1a 325	GIn	GIn	Lys	Гrр	Thr 330	Leu	Arg	Asp			

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					gtc Val 70						_			-		240
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atg	aaa	ctt	cat	cat	ggt	gag	aac	cgt	ctg	aag	aaa	ctc	atg	tgt	tgt	384

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	_		-				-			agc Ser						-		480
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		_				_			-	aac Asn	-			_	_	_	!	576
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			_	-			-	_		ttt Phe		_					I	672
			_	-				_		gag Glu					-			720
										gaa G1u 250								768
					Lys					aga Arg							;	816
										tgt Cys							1	864
,	ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	(	912

Leu	His 290	Leu	His	Gln	Asn	G1y 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly	
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														ttt Phe 335		1008
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	Gln	Met	Leu 20		Gly	Leu	Gly	G1n 25		Val	Leu	Leu	Asn 30	Asn	Ser	
Leu													~ ~			

		35					40					45			
Lys	Pro 50	Ser	Ser	Val	Phe	Arg 55	Asn	Gly	Phe	Ser	Gly 60	Ile	Lys	Lys	Pro
Trp 65	His	Arg	Cys	His	Val 70	Cys	Asn	His	His	Phe 75	Gln	Phe	Lys	Gln	His 80
Leu	Arg	Asp	His	Met 85	Asn	Thr	His	Thr	Asn 90	Arg	Arg	Pro	Tyr	Ser 95	Cys
Arg	Ile	Cys	Arg 100	Lys	Ser	Tyr	Val	Arg 105	Pro	Gly	Ser	Leu	Ser 110	Thr	His
		115					120					125	Met		-
Glu	Phe 130	Cys	Ala	Lys	Val	Phe 135	Gly	His	Ile	Arg	Val 140	Tyr	Phe	Gly	His
Leu 145	Lys	Glu	Val	His	Arg 150	Val	Val	Ile	Ser	Thr 155	Glu	Pro	Ala	Pro	Ser 160
G1u	Leu	Gln	Pro	Gly 165	Asp	Ile	Pro	Lys	Asn 170	Arg	Asp	Met	Ser	Val 175	Arg
Gly	Met	Glu	Gly 180	Ser	Leu	Glu	Arg	Glu 185	Asn	Lys	Ser	Asn	Leu 190	Glu	Glu
Asp	Phe	Leu 195	Leu	Asn	Gln	Ala	Asp 200	Glu	Val	Lys	Leu	G1n 205	IJе	Lys	Cys
	210					215					220		Lys		
Leu 225	Leu	Asp	Val	His	G1y 230	Glu	Glu	Ile	Glu	Gly 235	Arg	Leu	Gln	Glu	G1y 240
				245					250				Gln	255	
			260					265					G1u 270		
		275					280					285	Lys		
Leu	His 290	Leu	His	Gln	Asn	G1y 295	Val	Glu	Met	Leu	Met 300	G1u	Asn	Glu	Gly
305					310					315			Gly		320
Cys	Pro	Gly	Leu	His 325	Thr	Phe	Leu	Leu	Trp 330	Ser	His	Ser	Gly	Phe 335	Asn
			340					345					Leu 350		
His	Trp	Lys 355	His	Gln	His	Asn	Cys 360	Glu	Asp	Pro	Ser	Lys 365	Leu	Trp	Ala
Пe	Leu 370	Asn	Thr	Val	Ser	Asn 375	Gln	Gly	Val	Ile	G1u 380	Leu	Ser	Ser	Glu
Ala	Glu	Lys													

183

385

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		Gly											gaa Glu		384
	His	-	-	-				_		-		-	ttg Leu	_	432
													ttt Phe		480
									-				aga Arg 175		528
-		-			_			_			-		cat His		576
_					_	-	-		_	-			gtt Val	_	624
						_	-	_			_	_	ttt Phe		672
	_				-		-	-	_	-	-		aat Asn	•	720
					_			-		_			aaa Lys 255		768
													aaa Lys		816
													gat Asp		864

				tat Tyr 295			_					_	-	912
		-	-	tca Ser	-				_					960
				gaa Glu				,			_		-	1008
				cca Pro										1056
	-	_		tac Tyr	-		_		-		•			1104
		-	-	tgg Trp 375		-			-	-	-			1152
				gct Ala		-		-						1200
				aat Asn										1248
				gag Glu										1296
				aca Thr										1344
Tyr			Lys	cgt Arg 455			-	-		-	-			1392

-			-	_	-	aat Asn	-		_			_	_			1	440
						aat Asn	_		-			-	_	-		14	488
	-	_				aca Thr	-		-		_	-			-	1!	536
	-		-	_	-	agc Ser	_	-				-				15	584
						gta Val 535									_	16	632
						act Thr										16	680
_			_			acc Thr	_	_	-	-		_		_		17	728
	-	-				cgt Arg	_		_	-				-		17	776
						ctg Leu										18	824
						agc Ser 615					_	_	-	-	_	18	372
						gaa Glu										19	920

- •		-	att Ile		-	_	-		-		•		_			1968
_		-	gaa Glu 660	-			-					-				2016
cct Pro	tga *	,														2022
	<td>220&gt; 221&gt; 222&gt;</td> <td>673</td> <td>IANT</td> <td>573)</td> <td></td> <td>Acid</td> <td>i</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	220> 221> 222>	673	IANT	573)		Acid	i								
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Ala	Cys	Pro	His 20	Met	Ala	Thr	Cys	G1y 25	Asn	Va1	Leu	Phe	Glu 30	Gly	Arg	
Thr	Val	G1n 35	Leu	Gly	Lys	Leu	Cys 40	Cys	Thr	Gly	Val	G1u 45	Thr	Glu	Asp	
Asp	G1u 50		Thr	Glu	Ser	Asn 55	Ser	Ser	Val	Glu	Gln 60	_	Ser	Val	Glu	
Va1 65		Asp	Gly	Pro	Thr 70		His	Asp	Pro	Asp 75		Tyr	Ile	Glu	Ile 80	
	Lys	Asn	Thr	Lys 85	Ser	Val	Pro	Glu	Tyr 90	Ser	Glu	Val	Ala	Tyr 95		
Asp	Tyr	Phe	Gly 100		Ile	Pro	Pro	Pro 105		Lys	Glu	Pro	Ile 110		Glu	
Arg	Pro	Tyr 115	Gly	Val	Gln	Arg	Thr 120		Пe	Ala	Gln	Asp 125		.G1u	Arg	
	Ile 130		Gln	Ser	Asp	Ile 135		Asp	Arg	Val	Val 140		Asp	Leu	Asp	
		Asn	Tyr	Thr	Ile 150		Glu	Glu	Gly	Asp 155		Leu	Lys	Phe	Asn 160	

Ser	Lys	Phe	Glu	Ser 165		Asn	Leu	Arg	Xaa 170		Ile	Gìn	Ile	Arg 175	-
Asn	Glu	Tyr	Asp 180		Ile	Leu	Asn	Ser 185	Asp	He	Asn	Ser	Asn 190	His	Tyr
His	Gl'n	Trp 195		Tyr	Phe	Glu	Val 200	Ser	Gly	Met	Arg	Pro 205	•	Val	Alá
-	210					215	-		Lys		220				
225					230				Val	235					240
				245					Asp 250					255	
			260					265	Gly				270	_	
-	-	275					280		Phe			285	•	•	
	290					295			Thr		300				
305					310				Asn	315				,	320
				325					Ser 330					335	
			340					345	Asn	-	_		350		
		355					360		Leu			365			
	370					375			Lys		380			•	
Met 385	Ser	Asn	Asn	Pro	Thr 390	Ala	Gln	Ser	Leu	Arg 395	Glu	Ser	Tyr	He	Phe 400
Lys	He	Val	Pro	Met 405	Leu	Asn	Pro	Asp	Gly 410	Val	Ile	Asn	Gly	Asn 415	His
			420				·	425	Asn	_		•	430		
		435					440		His			445			
Tyr	Leu 450	Ala	Ala	Val	Lys	Arg 455	Leu	Pro	Leu	Val	Tyr 460	Cys	Asp	Tyr	His
G1y 465	His	Ser	Arg	Lys	Lys 470	Asn	Val	Phe	Met	Tyr 475	Gly	Cys	Ser	Пe	Lys 480
Glu	Thr	Val	Trp	His 485	Thr	Asn	Asp	Asn	A1a 490	Thr	Ser	Cys	Asp	Va1 495	Val
Glu	Asp	Thr	G1y 500	Tyr	Arg	Thr	Leu	Pro 505	Lys	Ile	Leu	Ser	His 510	Пe	Ala

Pro	Ala	Phe 515	Cys	Met	Ser	Ser	Cys 520	Ser	Phe	Val	Val	G1u 525	Lys	Ser	Lys	
Glu	Ser 530		Ala	Arg	Val	Val 535		Trp	Arg	Glu	I1e 540		Val	Gln	Arg	
Ser 545	Tyr	Thr	Met	G1u	Ser 550	Thr	Leu	Cys	G1y	Cys 555	Asp	Gln	Gly	Lys	Tyr 560	
Lys	Gly	Leu	Gln	I1e 565	Gly	Thr	Arg	Glu	Leu 570	Glu	Glu	Met	Gly	A1a 575	Lys	
Phe	Cys	Val	Gly 580	Leu	Leu	Arg	Leu	Lys 585	Arg	Leu	Thr	Ser	Pro 590	Leu	Glu	
Tyr	Asn	Leu 595	Pro	Ser	Ser	Leu	Leu 600	Asp	Phe	Glu	Asn	Asp 605	Leu	Пe	Glu	
Ser	Ser 610	Cys	Lys	Val	Thr	Ser 615	Pro	Thr	Thr	Tyr	Va1 620	Leu	Asp	Glu	Asp	
G1u 625	Pro	Arg	Phe	Leu	G1u 630	Glu	Val	Asp	Tyr	Ser 635	Ala	Glu	Ser	Asn	Asp 640	
Glu	Leu	Asp	Ile	G1u 645	Leu	Ala	Glu	Asn	Va1 650	Gly	Asp	Tyr	Glu	Pro 655	Ser	
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	tat Tyr															96
	ttt Phe															144

_		-				-							gcc Ala			192
		_	-										cct Pro			240
	_		-										gct Ala			288
_			-							-			gaa Glu 110			336
		_			_	cac His				_		tga *				375
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	Tyr	Ser	Leu 20		Val	Ala	Phe	Leu 25	Thr	Ile	Ser	Thr	Thr 30		Gly	
Gly	Phe	Cys 35		Ser	Gly	Phe	Ser 40		Asn	His	Leu	Asp 45	Ile	Ala	Pro	
Ser	Tyr 50		Gly	Пe	Leu	Leu 55		Пe	Thr	Asn	Thr 60		Ala	Thr	Ile	
Pro 65		Met	Val	Gly	Pro 70		Ile	Ala	Lys	Ser 75		Thr	Pro	Asp	Asn 80	
	Val	Gly	Glu	Trp 85		Thr	Val	Phe	Tyr 90		Ala	Ala	Ala	I1e 95		
Val	Phe	Gly	Ala 100		Phe	Phe	Thr	Leu 105		Ala	Lys	Gly	Glu 110		G1n	
Asn	Trp	Ala 115		Asn	Asp	His	His 120		His	Arg	His					

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191

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_		-	-	-		ttc Phe					_					96
-		_	_			cta Leu	_	_					-			144
			-		_	ttt Phe 55				_	-			-	-	192
-			-	-		999 Gly				-				-		240
_	_	-	-	-		cga Arg	-									288
						atg Met										336
cgt	ссс	cct	cga	tgt	tcc	cac	tgc	agt	gtc	tgt	gac	aac	tgt	gtg	gag	384

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Arg	Pro	Pro 115	Arg	Cys	Ser	His	Cys 120	Ser	Val	Cys	Asp	Asn 125	Cys	Val	Glu		
-		-			tgc Cys									-			432
					ttc Phe 150								-				480
-					ttt Phe					-							528
					cgc Arg												576
-					atc Ile		_	-			_						624
-	_		_		gga Gly	_				_	-	-	_				672
					aac Asn 230						_	-			-		720
_	_	_		-	agt Ser			-				_		_			768
-		_	_		att Ile	_		-					_				816
-		-		-	ata Ile			-		-	-				-	,	864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	1	912

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Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Ile	Thr	Glu	
-	_		-	_	-	gaa Glu								-	_	960
_	_				_	cga Arg					_	_				1008
-	-	-		_	-	aag Lys	-			-				-		1056
_			•			agt Ser	-	-	-	-		-	-	_	-	1104
						ttg Leu 375										1152
						agc Ser										1200
_	-	-			_	ttc Phe								-		1248
		-				agt Ser			_			-		_		1296
	G1n			-		gag Glu	-	-								1344
						tcc Ser 455		_	_	_			-		_	1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	1440

194

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 465 470 475 480 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu \* 485 490 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr Val Pro 5 Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe 25 Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met 55 60 Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 75 70 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile 85 90 Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr 105 Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asn Cys Val Glu 120 115 125 Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg 135 140 Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 150 155 Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 170 Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val 185 Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

		195					200					205			
Val	Leu 210	Val	Ala	Arg	Gly	Arg 215	Thr	Thr	Asn	Glu	G1n 220	Val	Thr	Gly	Lys
Phe 225		Gly	Gly	Val	Asn 230	Pro	Phe	Thr	Asn	G1y 235	Cys	Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245	Ser	Ser	Pro	Ala	Pro 250	Arg	Tyr	Leu	Gly	Arg 255	Pro
Lys	Lys	G1u	Lys 260	Thr	Ile	Val	Пe	Arg 265	Pro	Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	Пe	Thr	Va1 280	Lys	IJе	Met	Asp	Asn 285	Gly	Ile	Gln
•	290					295		•	•		300		Ile		
Ser 305	Gln	Ser	Ala	Asp	Ala 310	Glu	Pro	Pro	Pro	Pro 315	Pro	Lys	Pro	Asp	Leu 320
Ser	Arg	Tyr	Thr	Gly 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	Glu
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Ser	Ser 360	Ser	Ser	Thr	Ser	A1 a 365	Ala	Met	Pro
His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	Ile	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	Glu	Pro 400
Ser	Leu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
His	Phe	Asp	Pro 420	Leu	Ser	Ser	Gly	Ser 425	Arg	Ser	Ser	Ser	Leu 430	Lys	Ser
Xaa	Gln	G1y 435	Thr	Gly	Phe	Glu	Leu 440	Gly	Gln	Leu	Gln	Ser 445	Ile	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	A1a 460	Asn	G1n	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
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<213> Homo sapiens

<220>

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26

Cys Val Gly Ser Gly Thr Glu Ala Tyr Val Leu Val Leu Asp Pro His

20

25

30

tac tgg ggc act cca aaa agc ccc agt gaa cta cag gct gct ggg tgg
Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp
35 40 45

gtg ggc tgg caa gag gtg agt gca gcc ttt gac ccc aac tcc ttc tac

192
Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr

50

55

60

aac ctg tgc ttg acc agc ctt agc tcc caa cag cag cag cgc acc ttg
Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Gln Arg Thr Leu
65 70 75 80

gac tga 246 Asp \*

<210> 136

<211> 81

<212> PRT

<213> Homo sapiens

<400> 136

Met Val Gly Gly Asp Ala Asp Ala Arg Ser Lys Ala Leu Leu Gly Val 1 5 10 15

Cys Val Gly Ser Gly Thr Glu Ala Tyr Val Leu Val Leu Asp Pro His 20 25 30

Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp 35 40 45

Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr 50 55 60

Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Arg Thr Leu

65 Asp					70					75					80	
	< <	210> 211> 212> 213>	552 Dna		pien	S										
	<	220> 221> 222>		(	552)											
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		-					-	-	_		-			cca Pro		96
														tgg Trp		144
			_	-							_	-		gcc Ala	_	192
										_		_		tca Ser		240
								_	_	_	-		-	cag Gln 95	tct Ser	288
							-	_	-				_	gtc Val	-	336
										_	-			gtc Val	_	384

		115					120					125				
			tat Tyr											-	_	432
	Glu		gag Glu											_	-	480
			ggc Gly													528
			ctg Leu 180				tag *									552
		210> 211> 212> 213>	183	o sap	oiens	5										
Met 1		400> Gln	138 Arg	Leu 5	Ala	G1u	Phe	Arg	Ala 10	Ala	Arg	Lys	Arg		Gly	
_	Ala	Ala	G1n 20	_	Pro	Ala	Ala	Ser 25		Gly	Ala	Gln	Thr 30	15 Pro	Gly	
Glu	Lys	A1 a 35	Glu	Ala	Ala	Ala	Thr 40	Leu	Lys	Ala	Ala	Pro 45	Gly	Trp	Leu	
Lys	Arg 50	Phe	Leu	Val	Trp	Lys 55	Pro	Arg	Pro	Ala	Ser 60	Ala	Arg	Ala	Gln	
Pro 65	Gly	Leu	Val	Gln	G1u 70	Ala	Ala	Gln	Pro	G1n 75	Gly	Ser	Thr	Ser	Glu 80	
Thr	Pro	Trp	Asn	Thr 85	Ala	Ile.	Pro	Leu	Pro 90	Ser	Cys	Trp	Asp	G1n 95	Ser	
Phe	Leu	Thr	Asn 100		Thr	Phe	Leu	Lys 105		Leu	Leu	Trp	Leu 110		Leu	
Leu	Gly	Leu 115	Phe	Val	Glu	Leu	Glu 120		Gly	Leu	Ala	Tyr 125		۷al	Leu	
Ser	Leu 130		Tyr	Trp	Met	Tyr 135		Gly	Thr	Arg	Gly 140		Glu	Glu	Lys	
_ys		Gly	Glu	Lys	Ser		Tyr	Ser	Val	Phe		Pro	Gly	Cys	Glu	

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145																	
Leu Arg Pro Leu Ala Gly Arg 180 <pre></pre>			e Gln	Gly		Leu		Ala	G1u		Leu		Arg	Glu		Gln	
<pre> &lt;211&gt; 912 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  </pre> <pre> &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(912)  &lt;400&gt; 139 atg gcg gcg gcg gcg gca ttg ggc agc tcc tca ggc tcg gcg tcc ccg gcc Met Ala Ala Ala Ala Leu Gly Ser Ser Ser Gly Ser Ala Ser Pro Ala 1</pre>	Leu	Arg	Pro		Ala		Arg			1/0					1/5		
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Lys Leu Leu Leu Thr Tyr Ala Asp Asn Ile Leu Arg Asn Pro Asn Asp 40 45  gaa aaa tat aga tcc atc cgg att gga aac aca gcc ttt tct act aga 192 Glu Lys Tyr Arg Ser Ile Arg Ile Gly Asn Thr Ala Phe Ser Thr Arg 50 55 60  ctc ttg cct gtc aga gga gct gtt gaa tgt tta ttt gaa atg ggc ttt Leu Leu Pro Val Arg Gly Ala Val Glu Cys Leu Phe Glu Met Gly Phe 65 70 75 80  gaa gag gga gaa aca cat ctc atc ttt cct aaa aaa gct tca gtg gag Glu Glu Gly Glu Thr His Leu Ile Phe Pro Lys Lys Ala Ser Val Glu 90 95  cag ctg caa aaa att cgt gac ctg att gcc ata gag aga agt agc aga 336 Gln Leu Gln Lys Ile Arg Asp Leu Ile Ala Ile Glu Arg Ser Ser Arg	gtg Val	gct Ala	gag Glu	Leu	tgc Cys	cag Gln	aac Asn	acc Thr	Pro	gag Glu	acc Thr	ttt Phe	ttg Leu	Glu	gcc Ala	tcc Ser	96
Glu Lys Tyr Arg Ser Ile Arg Ile Gly Asn Thr Ala Phe Ser Thr Arg 50			Leu					Asp					Asn				144 ·
Leu Leu Pro Val Arg Gly Ala Val Glu Cys Leu Phe Glu Met Gly Phe 65 70 75 80  gaa gag gga gaa aca cat ctc atc ttt cct aaa aaa gct tca gtg gag Glu Glu Gly Glu Thr His Leu Ile Phe Pro Lys Lys Ala Ser Val Glu 85 90 95  cag ctg caa aaa att cgt gac ctg att gcc ata gag aga agt agc aga Gln Leu Gln Lys Ile Arg Asp Leu Ile Ala Ile Glu Arg Ser Ser Arg		Lys					Arg					Ala					192
Glu Glu Gly Glu Thr His Leu Ile Phe Pro Lys Lys Ala Ser Val Glu 85 90 95  cag ctg caa aaa att cgt gac ctg att gcc ata gag aga agt agc aga Gln Leu Gln Lys Ile Arg Asp Leu Ile Ala Ile Glu Arg Ser Ser Arg	Leu					Gly					Leu					Phe	240
Gln Leu Gln Lys Ile Arg Asp Leu Ile Ala Ile Glu Arg Ser Ser Arg					Thr					Pro					Val		288
				Lys					Пe					Ser			336

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				att Ile								62	4
				gct Ala								67	2
				ttg Leu 230								. 72	0
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Glu	Lys 50	Tyr	Arg	Ser	Пе	Arg 55	Ile	Gly	Asn	Thr	Ala 60	Phe	Ser	Thr	Arg	
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Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	He	Leu	Glu	Val ·	Leu 175	Gln	
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Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Пe	Asn	Ile	Ser	
Asp 225		Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys	Glu	G1u 240	•
	Phe	His	Trp	Val 245		Asn	Val	Leu	Cys 250	Ser	Lys	Cys	Gly	Gly 255	Gl'n	
Thr	Ara	Ser	Ara		Ara	Ser	Leu	Leu		Ser	Asp	Asp	Glu	Leu	Lvs	

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Trp	Gly	A1a 275		Glu	Val	Głu	Asp 280		Tyr	Cys	Asp	A1 a 285	Cys		Phe	
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						gag Glu									gaa Glu 80	240
						ggt Gly			-	-			-			288
						ggt Gly						Ala				336

				-	agt Ser					-			-			384
	-	-			gtt Val	-				Ĺys		_			•	432
_		_		_	aat Asn 150	_		-			-	_		-		480
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	-		-		att Ile			-	-		-			_		576
					aaa Lys								_			624
					ttg Leu			_				-	_	-	-	672
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Leu Thr Asp Gly Ser Tyr Asp Asp Val Leu Asn Ala Glu Gln Leu Gln
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Lys Leu Leu Tyr Leu Leu Glu Ser Thr Glu Asp Pro Val Ile Ile Glu
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Arg Ala Leu Ile Thr Leu Gly Asn Asn Ala Ala Phe Ser Val Asn Gln
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Ala Ile Ile Arg Glu Leu Gly Gly Ile Pro Ile Val' Ala Asn Lys Ile
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Asn His Ser Asn Gln Ser Ile Lys Glu Lys Ala Leu Asn Ala Leu Asn
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Leu Leu Arg Ala Gln Val Asp Ser Ser Phe Leu Ser Leu Tyr Asp Ser
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									gac Asp			
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480						Glu			gtg Val			
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Leu Ala Arg Ser Ser Leu His Gly Ile Ser Gln Val Val Lys Asp His Val Thr Lys Pro Thr Ala Met Ala Gln Gly Arg Val Ala His Leu Ile Glu Trp Lys Gly Trp Ser Lys Pro Ser Asp Ser Pro Ala Ala Leu Glu 55 Ser Ala Phe Ser Ser Tyr Ser Asp Leu Ser Glu Gly Glu Gln Glu Ala Arg Phe Ala Ala Gly Val Ala Glu Gln Phe Ala Ile Ala Glu Ala Lys 90 Leu Arg Ala Trp Ser Ser Val Asp Gly Glu Asp Ser Thr Asp Asp Ser 105 Tyr Asp Glu Asp Phe Ala Gly Gly Met Asp Thr Asp Met Ala Gly Gln 120 125 Leu Pro Leu Gly Pro His Leu Gln Asp Leu Phe Thr Gly His Arg Phe 135 Ser Arg Pro Val Arg Gln Gly Ser Val Glu Pro Glu Ser Asp Cys Ser 150 155 .Gln Thr Val Ser Pro Asp Thr Leu Cys Ser Ser Leu Cys Ser Leu Glu 165 170 Asp Gly Leu Leu Gly Ser Pro Ala Arg Leu Ala Ser Gln Leu Leu Gly 180 185 Asp Glu Leu Leu Ala Lys Leu Pro Pro Ser Arg Glu Ser Ala Phe 200 Arg Ser Leu Gly Pro Leu Glu Ala Gln Asp Ser Leu Tyr Asn Ser Pro 215 Leu Thr Glu Ser Cys Leu Ser Pro Ala Glu Glu Glu Pro Ala Pro Cys 230 235 Lys Asp Cys Gln Pro Leu Cys Pro Pro Leu Thr Gly Ser Trp Glu Arg 245 250 Gln Arg Gln Ala Ser Asp Leu Ala Ser Ser Gly Val Val Ser Leu Asp 260 265 Glu Asp Glu Ala Glu Pro Glu Glu Gln 275 <210> 145 <211> 1353 <212> DNA ' <213> Homo sapiens <220> <221> CDS <222> (1)...(1353)

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ctg Leu	999 Gly	ctg Leu	gaa Glu 20	ı Leu	tca Ser	aga Arg	tgc Cys	cgg Arg 25	ı Ala	aaa Lys	ccc Pro	cct Pro	. gga . G1y . 30	/ Arg	gcc Ala	96
			Pro					Phe					Tyr	cag Gln	gtc Val	144
							Asp					Pro		ctc Leu		192
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tcc Ser	ctt Leu	gtg Val	gat Asp 100	tgg Trp	ctg Leu	ggt Gly	cgc Arg	aag Lys 105	aat Asn	tct Ser	tgt Cys	gtc Val	ctc Leu 110	ttc Phe	tcc Ser	336
														tac Tyr		384
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tc he :	tca Ser	gcc Ala	ttc Phe	Glu·	gcc Ala 150	tgg Trp	tat Tyr	atc Ile	His	gag Glu 155	cac His	gtg Val	gaa Glu	cgg Arg	cat His 160	480
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				o Ile					Va1					Ala		atc Ile	624
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9	gct Na	cta Leu	ttt Phe	gag Glu 260	agt Ser	gtc Val	atc Ile	ttc Phe	atc Ile 265	ttt Phe	gtc Val	ttc Phe	ctc Leu	tgg Trp 270	aca Thr	cct Pro	816
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a I	tc le	gtc Val	gtc Val	ttc Phe	tct Ser 325	ctc Leu	ttc Phe	atg Met	Leu	act Thr 330	ttc Phe	tct Ser	acc Thr	agc Ser	cca Pro 335	ggc Gly	1008
				ccg Pro 340				Phe					Leu				1056

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						gct Ala 375						Phe					1152
	His					cta Leu											1200
						aat Asn			_		_		-	-	•		1248
						gtg Val						-	-	~ ~			1296
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Cys			20 Pro:	Ser	Phe	Leu		25 Phe	Gln	Leu	Asp		30 Tyr	Gln	Val	٠	
Tyr			Ala I	Leu		Ala . 55		Trp	Leu		A1a 60		Tyr	Leu	Tyr		

Lys 65	Leu	Tyr	Gln	His	Tyr 70	Tyr	Phe	Leu	Glu	Gly 75	Gln	He	Ala	Ile	Leu 80
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Leu	Thr	Tyr 115		Leu	.Cys	Cys	Leụ 120	Thr	Lys	Leu	Ser	Gln 125	•	Tyr	Phe
Val	Leu 130	Leu	Val	Gly	Arg	Ala 135		Gly	Gly	Leu	Ser 140	Thr	Ala	Leu	Leu
145	•				Ala 150	•				155				_	160
				165	Trp				170					175	
			180		Ala			185			•		190		
		195			Leu	-	200					205			
	210				Ala	215					220			•	
225					Arg 230					235		•			240
				245	Asp				250			_		255	
	٠.		260		Val			265					270		
		275			Gly		280					285			
	290				Leu	295					300				
305					Gln 310					315	-				320
				325	Leu				330					335	·
			340		Glu			345					350		
Ala	Cys	Gly 355	Leu	Tyr	Phe	Pro	Ser 360	Met	Ser	Phe	Leu	Arg 365	Arg	Lys	Val
Ile	Pro 370	Glu	Thr	Glu	Gln	A1a 375	Gly	Val	Leu	Asn -	Trp 380	Phe	Arg	Val	Pro
385					Cys 390					395					400
Arg	Lys	Thr	Gly	Thr 405.	Arg	Asn	Met		Ser 410	Ile	Cys	Ser	Ala	Val 415	Met

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Val	Met	: Ala	a Lei 420		ı Ala	a Val	۷a۱	G1y 425		Phe	. Thr	· Val	Val 430	_	His	
Asp	Ala	G1u 435		ı Arç	y Val	Pro	Ser 440	Pro		Glu	G]L	Pro 445	Tyr		Pro	•
Glu	Leu 450															
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									gag Glu							144
		Leu							aag Lys							192
									acc Thr						aga Arg 80	240
								_	cag Gln		-			_	_	288

						aat Asn			Gly								336
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Leu	Va1 50	Leu	Arg	Arg	Asp	Pro 55	Ser	Val	Lys	Arg	Thr 60		Cys	Arg	Gly		
Cys 65	Ser	Ser	Leu	Leu	Val 70	Pro	Gly	Leu	Thr	Cys 75		Gln	Arg	Gln	Arg 80		
٩rg	Cys	Arg	Gly	Gln 85	Arg	Trp	Thr	Val	G1n 90	Thr	Cys	Leu	Thr	Cys 95	Gln		
٩rg	Ser	Gln	Arg 100		Leu	Asn	Asp	Pro 105		His	Leu	Leu	Trp 110		Asp	•	
4rg	Pro	Glu 115			Leu	Gly	Ser 120		Ala	Asp	Ser	Lys 125		Leu	Gl'n		
Pro	Leu 130		Asn	Thr	Ala	His 135		Пe	Ser	Asp	Arg 140		Pro	Glu	Glu		
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			gag Glu											192	
	Ala		agg Arg											240	
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Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn
                         55
Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg
                                         75
Gly Val Val Cys Arg Leu Ser Arg Ser Leu Gln Glu His His Gly Leu
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Pro Pro Ala Gly Leu Cys Arg Gln Pro Ala Lys Ala Arg Pro Gln Asp
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                                 105
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192	ggc Gly	ctg Leu	tgg Trp	gtc Val	tgg Trp 60	aac Asn	cac His	ccc	cag G1n	ccc Pro 55	tcc Ser	acc Thr	ccc Pro	Asp	act Thr 50	gco Al a
240	ggc Gly 80	cct Pro	tcc Ser	cag Gln	cgg Arg	gac Asp 75	ctg Leu	cag Gln	cgc Arg	Ser	ctg Leu 70	gaa Glu	gag Glu	cag Gln	Asp	act Thr 65
288	999 Gly	gga Gly 95	gga Gly	999 Gly	agt Ser	gag Glu	tgt Cys 90	ccc Pro	tgc Cys	agc Ser	999 Gly	gag Glu 85	999 Gly	aag Lys	ccc Pro	ccg Pro
336	tcc Ser	agc Ser	acc Thr 110	acc Thr	ggc Gly	999 Gly	cct Pro	cct Pro 105	ggc Gly	ect Pro	gcc Ala	ctg Leu	acc Thr 100	cct Pro	gcc Ala	gag Glu
384	gta Val	cga Arg	aag Lys	cgg Arg 125	cgg Arg	999 Gly	999 Gly	gct Ala	gag Glu 120	aag Lys	cga Arg	gcc Ala	ctg Leu	acc Thr 115	agc Ser	tca Ser
432	gag Glu	gag Glu	cct Pro	tca Ser	cag Gln 140	gcc Ala	cca Pro	cct Pro	gcc Ala	cca Pro 135	gcg Ala	ttt Phe	aca Thr	gtg Val	ttt Phe 130	gag Glu
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Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
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Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
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Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
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Tyr			ccc Pro		Val					Ala							672
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rp			Gly	Ala				Glu .	Gln		Arg 60		His	Arg	Gln	
1e		Ser	Trn	Phe .			Hic !	Pro	Δra			Dha	G) v	ينم ا	∐ic .	

65					70		• .			75					80
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gt. Va	g tgg 1 Trj	g tg: o Tr:	g tad p Tyl 180	r Arç	g cc. g Pri	a tti o Phe	t caq e G1r	g tad n Tyr . 185	r Phe	t ga e Glu	a aag u Ly:	g aat s Asr	gto 1 Va <sup>-</sup> 190	l G1r	a gga n Gly		576
ati Ile	t gta e Val	a cct I Pro 195	o Arg	a tct J Ser	tad Tyr	cat His	tgg Trp 200	Pro	t tto Phe	ccc Pro	tgg Trp	cca Pro 205	Val	a gto I Val	cac His	•	624
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									cgg Arg								192
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									cat His								336

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Sei	r Al	a Se	r Sei	r Lei 85	u Hi	s Pro	o Sei	r Phe	e Ası 90	o Ası	э Туг	r Gli	u Lei	u Glr 95	n Ser	
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				cta Leu								384
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				ata Ile								528
				gca Ala						-	gaa · Glu	576
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	_		ttg Leu 100		_			_	Gly			-	-	_	_	336	
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													aaa Lys			144
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											gga Gly					576
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		Ala					Gly				atg Met					816
gag	ctc	999	gtc	ctt	ttc	ctc	cct	tca	gca	ttt	ggt	cta	gac	agt	ttc	864

Glu	Leu	Gly 275	۷a۱	Leu	Phe	Leu	Pro 280	Ser	Ala	Phe	Gly	Leu 285	Asp	Ser	Phe	
	gtg Val 290		_	-						-	_		-	-		912
	cct Pro					_			_	-			-		-	960
	cca Pro			_									-			1008
	aac Asn	-					tga *									1032
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1 Ser	Asn	Leu	Ile 20	5 His	Ala	Asp	Trp	His 25	10 Gln	Lys	Thr	Gln	G1y 30	15 Ile	Trp	
Leu	Ser	Pro 35		Tyr	Pro	Arg	Ile 40		Asp	Gly	Thr	His 45		Ser	Gly	
Glu	Ser 50		Thr	His	Phe	Lys 55		Asp	Leu	Пe	Ser 60		Leu	Met	Ala	
Tyr																
65	Asn	Ala	Pro	Ser	Leu 70	Lys	Glu	Trp	Ile	Asp 75	Val	He	His	Lys	His 80	
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Asp		Ser	Glu	Thr 85	70 Asn	Val	Tyr	Leu	Ile 90	75 <sup>°</sup> Gly	Ser	Thr	Pro	Gly 95	80 Arg	
Asp Phe	Leu	Ser Gly	Glu Ser 100	Thr 85 Gln	70 Asn Lys	Val Asp	Tyr Asn	Leu Trp 105	Ile 90 Gly	75 Gly His	Ser Phe	Thr Arg	Pro Leu 110	Gly 95 Lys	80 Arg Lys	

Lys 145	ırp	Leu	Lys	Ser	150	rne	Lys	Glu	Ser	met 155	Leu	ınr	Leu	GIY	Lys 160	
	Ser	Lys	Thr	Pro		Lys	Ser	Ser	Val		Leu	Tyr	Leu	Ile		
_				165				_	170			_	_	175		
Pro	Ser	Val	Glu 180	Asn	Val	Arg	Thr	Ser 185	Leu	Glu	Gly	Tyr	Pro 190	Ala	Gly	
Gly	Ser	Leu 195	Pro	Tyr	Ser	Ile	G1n 200	Thr	Ala	Glu	Lys	G1n 205	Asn	Trp	Leu	
His	Ser 210	Tyr	Phe	His	Lys	Trp 215	Ser	Ala	Glu	Thr	Ser 220	Gly	Arg	Ser	Asn	
	Met	Pro	His	He	-	Thr	Tyr	Met	Arg		Ser	Pro	Asp	Phe		
225 Lvs	ماآ	Δla	Trn	Dhe	230	Val	Thr	Ser	Δla	235 Asn	Leu	Ser	Lvc	Ala	240 Δ1a	
Lys	116	ΛIα	ΠP	245	Leu	vui	,,,,	501	250	7311	LCU	301	Lys	255	Aiu	
Trp	Gly	Ala	Leu 260	Glu	Lys	Asn	Gly	Thr 265	Gln	Leu	Met	Ile	Arg 270	Ser	Tyr	
Glu	Leu	G1y 275	Val	Leu	Phe	Leu	Pro 280	Ser	Ala	Phe	Gly	Leu 285	Asp	Ser	Phe	
Lys	Va1 290	Lys	G1n	Lys	Phe	Phe 295	Ala	Gly	Ser	Gln	G1u 300	Pro	Met	Ala	Thr	
Phe 305	Pro	Val	Pro	Tyr	Asp 310	Leu	Pro	Pro	Glu	Leu 315	Tyr	Gly	Ser	Lys	Asp 320	
Arg	Pro	Trp	Пe	Trp 325	Asn	He	Pro	Tyr	Val 330	Lys	Ala	Pro	Asp	Thr 335	His	
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ctg	ttg	gtg	ctg	<b>ggg</b>	gct	ссс	cta	gtg	ctg	gcc	ggc	gag	gac	tgc	ctg	96
Leu	Leu	Val	Leu 20	Gly	Ala	Pro	Leu	Va1 25	Leu	Ala	Gly	Glu	Asp 30	Cys	Leu	
			20					23					SU			

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-	-		_			acc Thr				_	-			_	_	240
						gca Ala										288
_	_		-	-		acc Thr		-	-			-		-	-	336
	_		-		_	cag Gln	_		_	_			-		_	384
			_			atc Ile 135			-		_					432
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Trp Tyr Leu Asp Arg Asn Gly Ser Trp His Pro Gly Phe Asn Cys Glu
Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
                        55
Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala
Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
                                105
Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
                        135
                                            140
Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
                    150
Pro Pro Ser Gly Pro Ala Pro Gln Tyr Pro Leu Tyr Pro Ala Gly Pro
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Pro Val Tyr Asn Pro Ala Ala Pro Pro Pro Tyr Met Pro Pro Gln Pro
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			tca Ser 100				-				-	_			-	336
			cca Pro		_	_	_		_	_		_	_			384
			act Thr													432
			ctc Leu													480
			ggt Gly													528

				Lys		gga Gly			Gly					Met		576
			Ser			tgt Cys										624
		Asn				cgg Arg 215				_	-	Trp	-	tag *		669
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Leu	Gly	Ala	Va1 20	Leu	His	Gly	Thr	Va1 25	Leu	Arg	His	Val	Ala 30	Asn	Pro	
Arg	Gly	A1a 35	Val	Thr	Pro	Glu	Tyr 40	Thr	Val	Ala	Asn	Val 45	Ile	Ser	Val	
Gly	Ser 50	Gly	Leu	Leu	Ser	Va1 55	Ser	Val	Gly	Leu	Val 60	Ala	Leu	Leu	Ala	
Ser 65	Arg	Asn	Leu	Leu	Arg 70	Pro	Pro	Leu	His	Trp 75	Val	Leu	Leu	Ala	Leu 80	
41a	Leu	Val	Asn	Leu 85	Leu	Leu	Ser	Val	Ala 90	Cys	Ser	Leu	Gly	Leu 95	Leu	
_eu	Ala	Val	Ser 100	Leu	Thr	Val	Ala	Asn 105	Gly	Gly	Arg	Arg	Leu 110	Ile	Ala	
Asp	Cys	His 115	Pro	Gly	Leu	Leu	Asp 120	Pro	Leu	Val	Pro	Leu 125	Asp	Glu	Gly	
Pro	Gly 130	His	Thr	Asp	Cys	Pro 135	Phe	Asp	Pro	Thr	Arg 140	Ile	Tyr	Asp	Thr	
A1a L45	Leu	Ala	Leu	Trp	Ile 150	Pro	Ser	Leu	Leu	Met 155		Ala	Gly	Glu	Ala 160	
41a	Leu	Ser	Gly	Tyr 165	Cys	Cys	Val	Ala	Ala 170		Thr	Leu	Arg	Gly 175		
aly	Pro	Cys	Arg	Lys	Asp	Gly		Gln	Gly	Gln	Leu	Glu	Glu	Met	Thr	

Glu	Leu	Glu 195		Pro	Lys	Cys	Lys 200	Arg	Gln	Glu	Asn	G1u 205		Leu	Leu		
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	Leu															,0	
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	cag Gln															144	
	acc Thr 50															192	
	att Ile		Leu	Thr												240	
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Tyr Lys \*

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Ser Thr Thr Val Ser Arg Lys Ala Trp Gly Ala Glu Ala Val Gly Cys
50 55 60

Ser Ile Gln Leu Thr Thr Pro Val Asn Val Leu Val Ile His His Val 65 70 75 80

Pro Gly Leu Glu Cys His Asp Gln Thr Val Cys Ser Gln Arg Leu Arg 85 90 95

Glu Leu Gln Ala His His Val His Asn Asn Ser Gly Cys Asp Val Ala 100 105 110

Tyr Lys

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		_						aag Lys	_		_		_			192
		-	_				-	aga Arg			-		-		-	240
	_		_			_	-	gga Gly				_	-		-	288
						_	-	aag Lys 105	_	-		-		_		336
-		-	_		_	_	-	tct Ser					-	_		384
	_	-			_			gcc Ala				_		_		432
				_				atg Met	_	-			-	-	-	480
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-	-							gag Glu 185	_							576
								ggc Gly								624

						cag Gln 215										672
						atg Met										720
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	gag Glu		tga *													924
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			20			Asn		25					30		-	
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Phe	Asn 50	Leu	Met	Phe	Ihr	Lys 55	Val	Lys	Leu	Glu	G1n 60	Val	Leu	Lys	Gly	•

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Thr Leu Tyr Ser Phe Ser Gln Leu Gly Gly Leu Glu Lys Asp Gly Ser
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Phe Gly Glu Gly Leu Thr Met Lys Lys Gln Ser Gly Met His Leu Thr
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Leu Pro Asp Ala His Asp Ala Asp Ser Gly Ser Arg Arg Ala Ser Ser
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Ile Ala Ala Ser Arg Leu Glu Glu Ala Met Ser Glu Leu Thr Met Pro
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Ser Ser Val Leu Lys Gln Gly Pro Met Gln Leu Trp Thr Thr Leu Glu
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Gln Ile Trp Leu Gln Ala Ala Glu Leu Phe Met Glu Gln Gln His Leu
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                                    170
Lys Glu Ala Gly Phe Cys Ile Gln Glu Ala Ala Gly Leu Phe Pro Thr
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Ser His Ser Val Leu Tyr Met Arg Gly Arg Leu Ala Glu Val Lys Gly
                            200
Asn Leu Glu Glu Ala Lys Gln Leu Tyr Lys Glu Ala Leu Thr Val Asn
                        215
Pro Asp Gly Val Arg Ile Met His Ser Leu Gly Leu Met Leu Ser Arg
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Leu Gly His Lys Ser Leu Ala Gln Lys Val Leu Arg Asp Ala Val Glu
                245
                                    250
Arg Gln Ser Thr Cys His Glu Ala Trp Gln Gly Leu Gly Glu Val Leu
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Gln Ala Gln Gly Gln Asn Glu Ala Ala Val Asp Cys Phe Leu Thr Ala
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	-		-			gag Glu									•	144
•						ctc Leu 55						-				192
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	-			-	_	acc Thr		_					-			288
					_	gtc Val				_						336
-						aca Thr	_	-		-						384
						gta Val 135				-		-			_	432
						aca Thr										480
gga	tca	aaa	ttt	gat	act	ggg	agc	ttt	gtt	ggt	ggt	att	gta	tta	acg	528

Gly Ser Lys Phe	Asp Thr 165	Gly Ser	Phe Val	_	Ile		Leu 175	Thr	
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aga aga ggc att Arg Arg Gly Ile 195					-	_			624
taa *									627
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Gly	Ser	Lys	Phe	Asp 165	Thr	Gly	Ser	Phe	Val 170	Gly	Gly	Ile	Val	Leu 175	Thr	
Leu	Gly	Val	Leu 180	Ser	Ile	Leu	Tyr	Ile 185	Gly	Cys	Lys	Met	Tyr 190	Tyr	Ser	
Arg	Arg	Gly 195	Ile	Arg	Tyr	Arg	Thr 200	Ile	Asp	Glu	His	Asp 205	Ala	He	Ile	
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							ggc Gly							-	-	96
							gtg Val 40									144
					_	-	cca Pro				-			_		192
							cag Gln									240

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														att Ile		;	384
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-	-	_	-	-	-		-		_				-	cag Gln 175		!	528
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														acc Thr		(	624
														ggc Gly			672
	_					_	-			-				gtc Val	•		720
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			gtg Val					_		•	•	816
			ctg Leu									864
			cgc Arg									912
			cga Arg 310			_		_	_		_	960
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			gcc Ala	-	-		-	-	_	-		1056
			tac Tyr									1104
			tat Tyr	-	_					_	•	1152
			ccc Pro 390					-	-	-	_	1200
		Пe	cga Arg									1248
	Leu		ggt Gly	Trp								1296

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agg gcc act gga aac tgt ccc agg aac gat gga ctc acg ctt ttg tcc
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tta aac tga
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Leu Asn *
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Trp Ile Ile Ile Ala Ala Thr Val Val Ser Ile Ile Ile Val Phe Asp
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Pro Leu Gly Gly Lys Met Ala Pro Tyr Ser Ser Ala Gly Pro Ser His
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                                            60
Leu Asp Ser His Asp Ser Ser Gln Leu Leu Asn Gly Leu Lys Thr Ala
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Ala Thr Ser Val Trp Glu Thr Arg Ile Lys Leu Leu Cys Cys Cys Ile
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Gly Lys Asp Asp His Thr Arg Val Ala Phe Ser Ser Thr Ala Glu Leu
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Phe Ser Thr Tyr Phe Ser Asp Thr Asp Leu Val Pro Ser Asp Ile Ala
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Ala Gly Leu Ala Leu Leu His Gln Gln Gln Asp Asn Ile Arg Asn Asn
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Gln Glu Pro Ala Gln Val Val Cys His Ala Pro Gly Ser Ser Gln Glu
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		195					200					205			
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I1e 225		His	Thr	Thr	G1y 230		Gln	Tyr	Arg	Asp 235	Phe	Пe	His	Val	Ser 240
Phe	His	Asp	Lys	Va1 245		Glu	Leu	Pro	Phe 250	Leu	Val	Ala	Leu	Asp 255	His
			Ser 260					265					270		
		275					280					285	·		
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305			Tyr		310					315					320
Phe	Ser	He	Ala	Pro 325	Glu	Tyr	Arg	Leu	Val 330	Ile	Val	Gly	His	Ser 335	Leu
Gly	Xaa	Gly	A1a 340	Ala	Ala	Leu	Leu	A1a 345	Thr	Met	Leu	Arg	A1a 350	Ala	Tyr
		355	Arg				360				•	365		•	
	370		Gln			375					380				
385			Val		390					395				·	400
			He	405					410					415	-
Lys	Ile	Leu	Leu 420	His	Gly	Leu	Trp	Tyr 425	Glu	Leu	Phe	Gly	G1 <i>y</i> 430	Asn	Pro
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			_		-		_			-		_		ttg Leu	-	144
_			-							-	_	-	-	cta Leu		192
	-			-				_			-	_	-	gtc Val		240
Ile		Asn	Ser	Gln	Leu		Пe	Trp	Xaa	Arg	Val	Ala		ctc Leu 95	Asn	288
														gta Val		336
	-				-				_		-		-	gaa Glu	-	384
tat	gat	tcc	ttt	tca	aat	cga	tgg	act	gaa	gtt	gct	ссс	ctt	aag	gaa	432

254

PCT/US00/29052

Tyr	Asp 130	Ser	Phe	Ser	Asn	Arg 135	Trp	Thr	Glu	Val	Ala 140	Pro	Leu	Lys	Glu		
-		_			-	gtg Val							_				480
					_	gat Asp			_		_	_	_				528
	_					tct Ser											576
-			_			gct Ala	-					_			_		624
_			_		-	gca Ala 215			_		_		_	-	-		672
		_		_	-	aat Asn			-								720
						aaa Lys											768
		Glu	_	Thr	_	act Thr	Пe		_		_		-		_	i	816
				_	_	gca Ala										i	864
-					_	tac Tyr 295				-				tga *			909

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Ile	Ile	Thr 275	260 Gly	Val	Ala	Ala	Met 280	265 Pro	Arg	Pro	Val	Ser 285	270 Tyr	His	Gly	
Cys	Va1 290		Ile	His	Arg	Tyr 295	Asn	Glu	Lys	Cys	Phe 300		Leu			
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							gta Val									96
_	_		_	_			ggc Gly 40						_	_		144
							cca Pro									192
_							gga Gly									240
		-				-	999 Gly	-			_				-	288

258

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gca atg gct ttc cag gtc cca ccc aac tca ccc cag ggg agt gtg gcc
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Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
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                                105
                                                     110
tgc ccg ccc cct cca gcc tac tgc aac acg cct ccg ccc ccg tac gaa
                                                                      384
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
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        115
                                                 125
cag gta gtg aag gcc aag tag
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Gin Val Val Lys Ala Lys *
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Pro Leu His Thr Glu Ala Val Val Leu Leu Val Pro Ser Asp Asp Gly
Arg Ala Phe Leu Leu Arg Xaa Gly Phe Phe Ile Arg Arg Arg Met Tyr
                                                 45
Pro Pro Pro Leu Ile Glu Glu Pro Ala Phe Asn Val Ser Tyr Thr Arg
Gln Pro Pro Asn Pro Gly Pro Gly Ala Gln Gln Pro Gly Pro Pro Tyr
                    70
                                        75
Tyr Thr Asp Pro Gly Gly Pro Gly Met Asn Pro Val Gly Asn Ser Met
                                    90
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
            100
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                                                     110
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
        115
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                                                125
Gln Val Val Lys Ala Lys
    130
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		212>														
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	<	220>														
	<	221>	CDS													
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				(												
	<	223>	n =	A,T	.C o	r G										
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Met	Glu	Arg	Ala	Phe	Gln	Thr	Ala	Leu	Trp	Leu	Leu	Gln	Pro	Glu	Val	
1				5					10					15		
gtc	ttc	atc	ctg	ggg	gat	atc	ttt	gat	gaa	999	aag	tgg	agc	acc	cct	96
Val	Phe	Ile	Leu	Gly	Asp	Пe	Phe	Asp	Glu	Gly	Lys	Trp	Ser	Thr	Pro	
			20					25					30			
nag	gcc	tgg	gcg	gat	gat	gtg	. gag	cgg	ttt	cag	aaa	atg	ttc	aga	cac	144
										-		_		Arg		
		35					40					45				
cca	agt	cat	gta	cag	ctg	aag	gta	gtt	gct	gga	aac	cat	gac	att	ggc	192
														He		
	50					55					60					
ttc	cat.	tat	gag	atg	aac	aca	tac	aaa	ata	gaa	cac	<b>†</b> ††	gag	aaa	ata	240
														Lys		۲۰۰
65		J			70		ŭ	-5		75	. 3				80	
++-	200	+-+	~~~	202	a+ a	+++	+-+	+~~							_4_	200
														gtg Val		288
iic.	301	JCI	ulu	85	LCu	THE	JC1	ijρ	90	uly	116	7311	THE	95	nec	
														tct		336
/aı	Asn	Ser		Ala	Leu	Asn	Gly		Gly	Cys	Gly	He	-	Ser	Glu	
			100					105					110			
														tcc		384
hr	Glu	Ala 115	Glu	Leu	He	Glu	Val	Ser	His	Arg	Leu	Asn	Cys	Ser	Arg	
		115					1 711					1 / 5				

				-							-	-	ccc Pro	_	432
			-	_	_				_			-	agt Ser	_	480
_											_		gac Asp 175		528
		_			-						_		caa G1n	_	576
_	_			_	_	-	_	_		_			acg Thr		624
-	-	_						_	_				agc Ser	_	672
			_	 						-			atg Met		720
-		_		-					-	-			cca Pro 255	_	768
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					aag Lys 295					tga *					900

261

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				245			_	_	250					255		
Glu	Asp	Val	Val 260		He	He	Tyr	Cys 265		Val	Val	Gly	Phe 270	Leu	Val	
Val	Leu	Thr 275		Thr	His	Phe	G1y 280		Leu	Ala	Ser	Pro 285		Leu	Ser	
Gly	Leu 290	Asn	Leu	Leu	Gly	Lys 295	Arg	Lys	Thr	Arg						
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													aaa Lys			144
tcc Ser	aaa Lys 50	tgt Cys	tct Ser	tct Ser	ttt Phe	ctg Leu 55	gat Asp	tat Tyr	gtc Val	aga Arg	cgg Arg 60	tct Ser	cta Leu	aag Lys	aag Lys	192
													atg Met			240
													ttt Phe			288
											_		ctt Leu	_	_	336

263

100 105 110 cga ctt tgt tac ctg aaa gag cag gaa gat att gca tgg tct gct ctt 384 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 115 120 125 gtg aag ttg ttt gat ccc gtg aaa tct ccc aga tgt tat gct gtt att 432 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 gcc ctg aag aag cag cag tga 453 Ala Leu Lys Lys Gln Gln \* 145 150 <210> 186 <211> 150 <212> PRT <213> Homo sapiens <400> 186 Met Ser Ala Cys Leu Ala Leu Glu Arg Val Ala Ala Gly Gln Gly Leu Pro Thr Glu Ser Leu Phe Tyr Arg Ala Val Leu Gln Asp Ile Ile Lys 25 Asp Cys Tyr Gly Ile Thr Lys Cys Asp Arg His Val Gly Lys Ile Tyr Ser Lys Cys Ser Ser Phe Leu Asp Tyr Val Arg Arg Ser Leu Lys Lys 55 60 Leu Gly Leu Asp Glu Ser Lys Leu Pro Glu Lys Ile Ile Met Asn Tyr Tyr Glu Lys Tyr Lys Pro Arg Met Asn Glu Leu Glu Ala Phe Asn Met 85 90 Leu Lys Val Val Leu Ala Pro Cys Ile Glu Thr Leu Ile Leu Leu Asp 105 110 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 Ala Leu Lys Lys Gln Gln 145 150 <210> 187 <211> 1491

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													ccc Pro		144
									 -	-		-	gcg Ala		192
													gtc Val		240
													gca Ala 95		288
		_						_	_		•		tca Ser		336
													gca Ala		384
													gcc Ala		432

-					cca Pro 150										480
_				_	aaa Lys						-	-			528
	-			-	ggt Gly		-				-	_			576
-		-			gag Glu										624
		-			gca Ala					 -		-			672
	_		-		atc Ile 230				-			-	-		720
	_	_			ttt Phe					 			-		768
_		_			gga Gly	_		_	-	 	-	-		;	816
					ctc Leu									,	864
					gtt Val									,	912
-					att Ile 310									,	960

		_		-	-	-	_			acc Thr	_		-		1008
										gtt Val		_			1056
-	-									gaa Glu				-	1104
	-	_	_	_	-					ttc Phe 380		_	-	-	1152
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			-		_	-			_	 gca Ala					1296
_				_		-				gta Val					1344
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267

tag 1491

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			260					265					270			
Leu	Gln	Arg 275	Lys	Arg	Leu	Leu	G1u 280	Val	Val	Thr	Ser	Ile 285	Ser	Asp	Ile	
Pro	Thr 290	Gly	Ile	Pro	Val	His 295	Leu	Glu	Leu	Ala	Ser 300	Met	Thr	Asn	Arg	
G1u 305	Leu	Met	Ser	Ser	Ile 310	Val	His	Gln	Val	Phe 315	Pro	Ala	Val	Thr	Ser 320	
	Gly	Leu	Asn	G1u 325	Gln	Glu	Leu	Leu	Phe 330	Leu	Thr	Gln	Ser	A1a 335		
Gly	Pro	His	Ser 340	Ser	Leu	Ser	Ser	Trp 345	Asn	Gly	Val	Pro	Asp 350	Val	Gly	
Met	Val	Ser 355	Asp	Пe	Leu	Phe	Trp 360	Ile	Leu	Lys	Glu	His 365		Arg	Ser	
Lys	Ser 370	Arg	Ala	Ser	Asp	Leu 375	Thr	Arg	Ile	His	Phe 380	His	Thr	Leu	۷a٦	
Tyr 385	His	Ile	Leu	Ala	Thr 390	Val	Asp	Gly	His	Trp 395	Ala	Asn	Gln	Leu	Ala 400	
Ala	Val	Ala	Ala	Gly 405	Ala	Arg	Val	Ala	Gly 410	Thr	Gln	Ala	Cys	Ala 415	Thr	
G1ụ	Thr	Ile	Asp 420	Thr	Ser	Arg	Val	Ser 425	Leu	Arg	Ala	Pro	G1n 430	Glu	Phe	
Met	Thr	Ser 435	His	Ser	G1u	Ala	Gly 440	Ser	Arg	Ile	Val	Leu 445	Asn	Pro	Asn	
Lys	Pr,o 450	Val	Val	Glu	Trp	His 455	Arg	Glu	Gly	Ile	Ser 460	Phe	His	Phe	Thr	
Pro 465	Val	Leu	Val	Cys	Lys 470	Asp	Pro	Ile	Arg	Thr 475	Val	Gly	Leu	Gly	Asp 480	
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-t-		\00>		++~	<b>t</b> 0 0	000	cct	+++		+00	+ - +	2+2	20+	aca	00±	40
														gcg Ala 15		48

269

				-		ccc Pro									96
						gca Ala					_		-		144
_	_	_				999 Gly 55	_	 _	_						192
						aag Lys								agt Ser 80	 240
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		-	-	-	-	gac Asp			-	-		-	_	_	336
tga *															339

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<211> 112

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<213> Homo sapiens

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65 Pro	Trp	Thr	Ile		70 G1n	Met	Val	Ile	75 Leu	Ser	Ile	Ala		80 Trp	
Gly	Ile	Val	Val 100		Ala	Asp	Pro	Lys 105	Lys	Ala	Tyr	Arg 110	95 Val	Val	
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												cag G1n			144
												tca Ser			192
												aga Arg			240
												999 Gly			288
												tgg Trp 110			336

	tct Ser			-						-		_			•		384
	gag Glu 130																432
	acg Thr																480
	gcc Ala														_	•	528
-	ttc Phe							_	-		•		_	_			576
	cag Gln																624
ttg Leu	tga *																630
	<2 <2	210> 211> 212> 213>	209	sap	oiens	i									٠		
Mad		00>		M - 4	A7 -	۸٦.	c	•				<b>T</b> 1		0.1			
Met 1	Ala	AIA	AIA	Met 5	Ala	Ala	ser	ser	Leu 10	ınr	val	ihr	Leu	G1y 15	Arg		
Leu	Ala	Ser	Ala 20	Cys	Ser	His	Ser	Ile 25	Leu	Arg	Pro	Ser	Gly 30	Pro	Gly		
Ala	Ala	Ser 35		Trp	Ser		Ser 40		Arg	Phe	Asn	Ser 45		Ser	Thr		
Ser	Tyr 50		Pro	Gly				Lys	Thr	Ser	Leu 60		Ser	Pro	Pro		
Trp	Pro	Glu	Val	Val			Asp	Pro	Val	Glu		Thr	Arg	His	His		

65					70					75					80	
Ala	Glu	Val	Val	Lys 85	Lys	Val	Asn	Glu	Met 90	Ile	Val	Thr	Gly	G1n 95	Tyr	
Gly	Arg	Leu	Phe 100	Ala	Val	Val	His	Phe 105	Ala	Ser	Arg	Gln	Trp 110	Lys	Val	
Thr	Ser	Glu 115	Asp	Leu	Ile	Leu	Ile 120	Gly	Asn	Glu	Leu	Asp 125	Leu	Ala	Cys	
Gly	Glu 130	Arg	Ile	Arg	Leu	G1u 135	Lys	Val	Leu	Leu	Val 140	Gly	Ala	Asp	Asn	
Phe 145	Thr	Leu	Leu	Gly	Lys 150	Pro	Leu	Leu	Gly	Lys 155	Asp	Leu	Val	Arg	Val 160	
Glu	Ala	Thr	Val	Ile 165	Glu	Lys	Thr	Glu	Ser 170	Trp	Pro	Arg	Ile	Ile 175	Met	
Arg	Phe	Arg	Lys 180	Arg	Lys	Asn	Phe	Lys 185	Lys	Lys	Arg	Ile	Val 190	Thr	Thr	
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Leu																
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	<4	<001	193													
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	gcg Ala											-		_		144
-	tgt Cvs	-					-		_							192

273

50 55 60 gtg tac tgg gtg gca cgg aag ccc atg aag atg gga tac ccc ccg agt 240 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 65 75 70 cca tgg acc att acg cag atg gtc atc ggc ctc agt gag aat caa ggc 288 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 85 90 att gcc acc tgg ggt atc gtt gtc atg gca gac ccc aaa ggg aag gcc 336 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 tac cgc gtt gtt tga 351 Tyr Arg Val Val \* 115 <210> 194 <211> 116 <212> PRT <213> Homo sapiens <400> 194 Met Gly Ser Arg Leu Ser Gln Pro Phe Glu Ser Tyr Ile Thr Ala Pro 5 10 15 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 25 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 55 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 70 75 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 85 90 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 110 Tyr Arg Val Val 115 <210> 195 <211> 1047

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		_	cct Pro	-				_			_			-		144
	-		ctc Leu	_		-	_	_		_	-		-	_	-	192
			gcg Ala													240
			gtg Val													288
			gtc Val 100													336
	_		gag Glu	_				_	_		_		_			384
			gaa Glu													432

						gac Asp										480
	_			-		gag Glu	_				-					528
	-					atg Met		_	_		-	-		-		576
						act Thr										624
-			-	-	_	gcc Ala 215						_			_	672
		-				ttg Leu	-	_	-	-		_		_	-	720
						acc Thr	-	-	-							768
		-			-	gcc Ala	-					-	-		ctg Leu	816
-		_				att Ile			•				_	_	-	864
_		-		_		caa G1n 295	-	-							_	912
	_			_		gac Asp		_		-						960

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 1047 tgg cta att cca gga caa gag cag gaa cat gtg gag tag Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu \* 340 345 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 130 135 140 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 145 150 155 160 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 165 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 180 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 195 200 205 Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala 215 Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

225					230					235					240		
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Val 250	Pro	Asn	He	Leu	Leu 255	Phe		
Gln	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265	Asn	His	Thr	Asp ·	Arg 270	Thr	Leu		
Glu	Thr	Leu 275	Lys	Ile	Phe	Ile	Phe 280	Asn	Gìn	Thr	Gly	Ile 285	Glu	Ala	Lys		
Lys	Asn 290	Val	Val	Val	Thr	G1n 295	Ala	Asp	Gln	Ile	Gly 300	Pro	Leu	Pro	Ser		
Thr 305	Leu	Пe	Lys	Ser	Val 310	Asp	Trp	Leu	Leu	Val 315	Phe	Ser	Leu	Phe	Phe 320	•	
Leu	Ile	Ser	Phe	I]e 325	Met	Tyr	Ala	Thr	11e 330	Arg	Thr	Glu	Ser	Ile 335	Arg		
Trp	Leu	Ile	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu						
	<2 <2	210> 211> 212> 213>	444 DNA	o sap	oiens	5											
	<2	220> 221> 222>		(4	144)												
_	gcc		cca			aaa Lys											48
						gga Gly									-		96
		-				aaa Lys	_	_			_						144
						ggc Gly 55										-	192
						gtg Val											240

65					70					75					80		
				-		_	_	_	-	_			cag Gln	_	_		288
_				-	_							-	gtc Val 110		_		336
-				-					-		-		aat Asn				384
													act Thr				432
	ctg Leu		tga *														444
	<2 <2	210> 211> 212> 213>	147	sap	oiens	<b>S</b>										٠.	
		l00>															
Met 1	Ala	Phe	Pro	Lys 5	Lys	Lys	Leu	Gln	Gly 10	Leu	Val	Ala	Ala	Thr 15	Ile		
Thr	Pro	Met	Thr 20	Glu	Asn	Gly	G1u	Ile 25	Asn	Phe	Ser	Val	Ile 30	Gly	Gln		
Tyr	Val	Asp 35		Leu	۷a٦	Lys	Glu 40		Gly	Val	Lys	Asn 45	Ile	Phe	Val		
Asn	Gly 50		Thr	Gly	Glu	Gly 55	. •	Ser	Leu	Ser	Va1 60		Glu	Arg	Arg		
G1n 65		Ala	Glu	Glu	Trp 70		Thr	Lys	Gly	Lys 75		Lys	Leu	Asp	G1n 80		
	Ile	Пе	His	Va1 85		Ala	Leu	Ser	Leu 90		Ġlu	Ser	Gln	G1u 95			
Ala	Gln	His	Ala 100		Glu	Пe	Gly	Ala 105		G1y	Ile	Ala	Val 110		Ala		
Pro	Phe	Phe		Lys	Pro	Trp	Thr		Asp	Ile	Leu	He	Asn	Phe	Leu		

·	Glu 130 Leu		Ala	Ala	Ala	Pro 135	120 Leu	Pro	Cys	His	Phe 140	125 Ile	Thr	Ile	Thr	
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	<2	220> 221> 222>		(7	705)											
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-	atg		caa		_	_		_						tat Tyr 15		48
	_	-	-		_		_	-						ttg Leu		96
	_	-					-	_	-	_	_	_		gtg Val	-	144
-					-									gtt Val		192
														tcc Ser		240
		-					-					_		ctg Leu 95		288

280

			-	-		tat Tyr			-		_		_		;	336
		-				cct Pro					_		_	-		384
_	_				-	cct Pro 135			-			-			4	432
						tgg Trp									4	480
	_	_	_	_		cgg Arg								-	Ę	528
				-	-	ctg Leu				-	-				Ę	576
-					_	gtt Val		_				_			6	524
	-		_			gtt Val 215			-		-	•	_		6	572
-		_		-		gac Asp	-	_	tga *						7	705

<210> 200

<211> 234

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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<210> 201

<211> 885

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(885)

			_											
<	222>	mis (1) n =	(	885)										
<	400>	201												
ctg Leu	gct	gtg									-			48
cgc Arg									_		_		_	96
cgc Arg				-	-			-		_		_		144
cgc Arg 50							_	-				-	-	192
aat Asn														240
gat Asp		-				-		_	-	_				288
gag Glu													_	336
aca Thr														384
tgt Cys 130													_	432
ttt Phe														480

283

									agg Arg					528
				 -	-	-	_	_	ctt Leu	•				576
									ggt Gly 205					624
									aaa Lys					672
									tgt Cys					720
-			-			_			ctg Leu	_	-	-		768
									gga Gly				1	816
									ctc Leu 285					864
Glu	_	gga Gly		tga *										885

<210> 202

<211> 294

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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	<;	220> 221> 222>		(8	861)											
_	<br gag Glu	_	aaa	-		_	_	-	_	-		-		_	-	48
	gtt Val			_	-		_	_					-	_	-	96
	ctc Leu		_	_			-			-						144
	tct Ser 50	_										_	_	_	_	192
_	gct Ala													_		240
_	ctg Leu					-			-	-	_					288
	gac Asp	-														336
	ccc Pro															384
	cca Pro	-			-				-							432

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286

130		-	135				140					
aga atc Arg Ile 145	_	_							-	-		480
cta aag Leu Lys	_	_										528
ctc tgc Leu Cys												576
gat gat ( Asp Asp (				g Cys								624
ttt ggt ( Phe Gly / 210	_	_										672
gag aat ( Glu Asn ( 225												720
cat ggt His Gly	•								-		_	768
cat cga ( His Arg		-			_	_	-	_	-		-	816
acc ttt ( Thr Phe /		_	_	p Pro						tga *		861

<210> 204

<211> 286

<212> PRT

<213> Homo sapiens

287

	<	400>	204												
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Pro	Val	Lys	Ser 20	Gln	Ala	Ile	Ala	G1n 25	Pro	Ala	Thr	Thr	Ala 30	Lys	Ser
His	Leu	His 35	Gln	Lys	Pro	Gly	G1n 40	Thr	Trp	Lys	Asn	Lys 45	Glu	His	His
Leu	Ser 50	Asp	Arg	Glu	Phe	Val 55	Phe	Lys	Glu	Pro	G1n 60	Gln	Val	Val	Arg
Arg 65	Ala	Pro	Glu	Pro	Arg 70	Val	Ile	Asp	Arg	G1u 75	Gly	Val	Tyr	Glu	11e 80
Ser	Leu	Ser	Pro	Thr 85	Gly	Val	Ser	Arg	Va1 90	Cys	Leu	Tyr	Pro	Gly 95	Phe
	·		Lys 100				-	105					110		·
		115	Lys				120				,	125			
	130	•	Leu			135	Ť	•			140	Ť		-	
145			Met		150				·	155				•	160
	-		Arg	165					170					175	
			Leu 180					185					190		
		195	Pro				200					205			
	210		Thr	_		215					220				
225		-	Asp		230	-				235	-				240
	-		Leu	245				·	250				·	255	
	_		Pro 260					265				_	270	Asn	Leu
Thr	Phe	Arg 275	Thr	Val	Tyr	Pro	Asp 280	Pro	Arg	Gly	Ala	Pro 285	Trp		

<210> 205

<211> 561

<212> DNA

<213> Homo sapiens

<220>

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289

caq qtq ctc cct gtg ttg aaa gag aat gtg gaa gqt cat gat tta cct 528 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 175 561 gca tct gag aaa cac cag gat gtt acc tcc taa Ala Ser Glu Lys His Gln Asp Val Thr Ser \* 180 185 <210> 206 <211> 186 <212> PRT <213> Homo sapiens <400> 206 Met Ile His Trp His Ser Glu Lys Ala Thr Leu Leu Leu Asn Ala Pro 10 Ser Phe Ser Asp Gln Leu Pro Gly Thr Met Ala Thr Leu Ser Leu Val 25 Asn Glu Ala Gln Tyr Leu Leu Ile Asn Thr Ser Ser Ile Leu Glu Leu 40 His Arg Gln Leu Asn Thr Ser Asp Glu Asn Gly Lys Glu Glu Leu Phe Ser Leu Lys Asp Leu Ser Leu Arg Phe Arg Ala Asn Ile Ile Asn 70 75 Gly Lys Arg Ala Phe Glu Glu Glu Lys Trp Asp Glu Ile Ser Ile Gly Ser Leu Arg Phe Gln Val Leu Gly Pro Cys His Arg Cys Gln Met Ile 105 Cys Ile Asp Gln Gln Thr Gly Gln Arg Asn Gln His Val Phe Gln Lys Leu Ser Glu Ser Arg Glu Thr Lys Val Asn Phe Gly Met Tyr Leu Met 135 140 His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser 150 155 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 175 Ala Ser Glu Lys His Gln Asp Val Thr Ser 180 185 <210> 207 <211> 1272 <212> DNA <213> Homo sapiens

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	_		_	-		atc Ile		-						-	-	96
				-		atc Ile			-	-			-	_	_	144
-	-			_		atg Met 55		-	_	-	-	-	-			192
			-		_	gta Val					-		_			240
-	• -			_		ttc Phe	_			_	_	_			-	288
						act Thr										336
				-		gga Gly		-			-		-	_		384
						gcg Ala	-	-						-		432

	130				135					140						
_				cac His 150	_			-					-		•	480
				 cat His			-		-	_				-	!	528
				atc Ile						-					!	576
	-		-	gct Ala	-	-				-	-				(	624
	-			gaa Glu				-			-				(	672
	_	-		caa G1n 230			_			-		_	_		,	720
				att Ile										-	7	768
	-	-		ttc Phe	-				-	-					3	316
				 gta Val							_				8	364
				tta Leu			-	-	-	-				_	9	912
				cct Pro			_					-	-		<u>.</u>	960

292

305 310 315 320 aca tgg ata gta act caa gta gca ata agt tac aca gtt gtg cca ttt 1008 Thr Trp Ile Val Thr Gln Val Ala Ile Ser Tyr Thr Val Val Pro Phe 325 330 335 gtg ctt ctt tct ata aaa cca tca ctc acg ttt tac agc tcc tgg tat 1056 Val Leu Leu Ser Ile Lys Pro Ser Leu Thr Phe Tyr Ser Ser Trp Tyr 345 340 350 tat tgc ctg cac att ctt ggt atc tta gta tta ttg ttg ttg cca gtg 1104 Tyr Cys Leu His Ile Leu Gly Ile Leu Val Leu Leu Leu Pro Val 355 360 365 aaa aaa act caa aga aga aag aat aca cat gaa aac att cag ctc tca 1152 Lys Lys Thr Gln Arg Arg Lys Asn Thr His Glu Asn Ile Gln Leu Ser 370 375 380 caa too aaa aag ttt gat gaa gga gaa aat tot ttg gga cag aac agt 1200 Gln Ser Lys Lys Phe Asp Glu Gly Glu Asn Ser Leu Gly Gln Asn Ser 385 390 ttt tct aca aca aac aat gtt tgc aat cag aat caa gaa ata gcc tcg 1248 Phe Ser Thr Thr Asn Asn Val Cys Asn Gln Asn Gln Glu Ile Ala Ser 405 410 415 aga cat tca tca cta aag cag tga 1272 Arg His Ser Ser Leu Lys Gln \* 420 <210> 208 <211> 423 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(423) <223> Xaa = Any Amino Acid <400> 208 Met His Asn Tyr Cys Phe Val Phe Ala Leu Gly Tyr Leu Thr Val Cys 5 1 10 15

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Phe	Ser	G1y 35		Met	Met	Пe	Ile 40	Thr	Gln	Lys	Ile	Thr 45	Ser	Leu	Ala
Cys	Glu 50	Пe	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	G1u 60	Glu	Leu	Thr	Ser
Ser 65	Gln	Arg	Asp	Leu	Ala 70	Val	Arg	Arg	Met	Pro 75	Ser	Leu	Leu	Glu	Tyr 80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	Ile 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
Ser	Tyr	Lys	Asp 100	Tyr	Пe	Thr	Phe	Ile 105	Glu	Gly	Arg	Ser	Tyr 110	His	Ιle
		115	_				Lys 120					125			
	130					135	Val			-	140			•	_
Leu 145	Ser	Leu	Leu	Phe	His 150	Leu	Thr	Ile	Cys	Thr 155	Thr	Leu	Pro	Val	G1u 160
Tyr	Asn	Пe	Asp	G1u 165	His	Phe	Gln	Ala	Thr 170	Ala	Ser	Trp	Pro	Thr 175	Lys
Ile	Ile	Tyr	Leu 180	Tyr	Ile	Ser	Leu	Leu 185	Ala	Ala	Arg	Pro	Lys 190	Tyr	Tyr
Phe	Ala	Trp 195	Thr	Leu	Ala	Asp	Ala 200	He	Asn	Asn	Ala	A1 a 205	Gly	Phe	Gly
Phe	Arg 210	Gly	Tyr	Asp	Glu	Asn 215	Gly	Ala	Ala	Arg	Trp 220	Asp	Leu	Ile	Ser
Asn 225	Leu	Arg	Ile	Gln	G1n 230	Ile	Glu	Met	Ser	Thr 235	Ser	Phe	Lys	Met	Phe 240
	•			245			Thr		250	·				255	
		•	260				Pro	265					270		
Ala	He	Trp 275	His	Gly	Val		Pro 280		Tyr		Leu		Phe	Leu	Thr
Gly	Va1 290	Leu	Met	Thr	Leu	A1 a 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn	Phe	Arg
His 305	Tyr	Phe	Пe	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	Ile 320
Thr	Trp	He	Val	Thr 325	Gln	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340	Пe	Lys	Pro	Ser	Leu 345	Thr	Phe	Tyr	Ser	Ser 350	Trp	Tyr
Tyr	Cys	Leu 355	His	He	Leu	Gly	Ile 360	Leu	Val	Leu	Leu	Leu 365	Leu	Pro	Val

Lys	Lys 370		Gln	Arg	Arg	Lys 375	Asn	Thr	His	Glu	Asn 380	Ile	Gln	Leu	Ser	
G1n 385	Ser		Lys	Phe	Asp 390	Glu	Gly	Glu	Asn	Ser 395		Gly	G1n	Asn	Ser 400	
Phe	Ser	Thr	Thr	Asn 405	Asn	Val	Cys	Asn	G1n 410	Asn	Gln	Glu	Ile	Ala 415		
Arg	His	Ser	Ser 420	Leu	Lys	Gln										
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	<	220> 221> 222>		(	1413	)										
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		-	_		_	Leu			-	-	_		-		•	40
_	_			-	-	ggc Gly				_	_				_	96
						cag Gln					_	_	-	_		144
Asn		Leu	Asp	Tyr	Thr	cag Gln 55	Thr		-			-			-	192
						ggt Gly										240
						cag G1n										288
gtg	ctg	acc	agc	ctt	gtg	gcg	ctg	cgg	cgg	gag	gtg	gag	gag	ctg	aga	336

	Val	Leu	Thr	Ser 100	Leu	Val	Ala	Leu	Arg 105	Arg	Glu	Val	Glu	Glu 110	Leu	Arg		
	-						gcg Ala		_		-			_	-	-	•	384
		-	-			_	aga Arg 135		_			_			_		4	432
	-				-		tcc Ser									_	4	480
	-		-		-	_	ttc Phe		-	-		_	-					528
			-				tct Ser	-				-		-		-	į	576
							gaa Glu										•	524
							ttg Leu 215	-							-		•	572
	-	-	-		=		ggt Gly				_		-		-		7	720
							gag Glu										7	768
					-	_	ctg Leu				_	_				-	8	316
(	cgg	cag	gac	ttt	ctc	tgg	cgc	ctg	gcc	cga	gcc	tac	agt	gac	atg	tgt	8	364

Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys	
														gat Asp		912
	-	_	-										-	gct Ala	-	960
_		_			-	_				-	_	-		cat His 335		1008
_		-		_		_	-			-		_		cat His		1056
-		_		_		_		-			_	_		ttt Phe		1104
				-		-	-			-	-			gaa G1u		1152
		-		-	-		-	-			-	-		gtg Val	-	1200
-	-		-	-			-	-	-			_		gga Gly 415		1248
		Ala							_			_	-	cta Leu		1296
			-	-		_		_	-	_	-	-		ctg Leu		1344
gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

297

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Leu	Leu	Gln	Gln	A1a 245	Asp	Glu	Leu	His	Arg 250	Gly	Asp	Glu	Gln	G1y 255	Lys		
Arg	Glu	Gly	Phe 260		Leu	Leu	Leu	Asn 265	Asn	Lys	Leu	Val	Tyr 270		Ser		
Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys		
Glu	Leu 290	Thr	Glu	Glu	Val	Ser 295	Glu	Lys	Lys	Ser	Tyr 300	Ala	Leu	Asp	Gly		
Lys 305	Glu	Glu	Ala	Glu	Ala 310	Ala	Leu	Glu	Lys	Gly 315	Asp	Glu	Ser	Ala	Asp 320		
Cys	His	Leu	Trp	Tyr 325	Ala	Val	Leu	Cys	Gly 330	Gln	Leu	Ala	Glu	His 335	Glu		
	Ile		340					345				-	350				
·	Lys	355					360					365			,		
Leu	G1y 370	Arg	Trp	Cys	Tyr	G1n 375	Val	Ser	His	Leu	Ser 380	Trp	Leu	Glu	Lys		
Lys 385	Thr	Ala	Thr	Ala	Leu 390	Leu	Glu	Ser	Pro	Leu 395	Ser	Ala	Thr	Val	G1u 400		
	Ala	Leu	Gln	Ser 405		Leu	Lys		Glu 410		Leu	Gln	Pro	Gly 415			
Ser	Lys	Ala	G1y 420	Arg	Val	Tyr	Пe	Ser 425	Lys	Cys	Tyr	Arg	G1u 430	Leu	Gly		
Lys	Asn	Ser 435	Glu	Ala	Arg	Trp	Trp 440	Met	Lys	Leu	Ala	Leu 445	Glu	Leu	Pro		
Asp	Va1 450	Thr	Lys	Glu	Asp	Leu 455	Ala	Ile	Gln	Lys	Asp 460	Leu	Glu	Glu	Leu		
G1u 465	Val	Пe	Leu	Arg	Asp 470												
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		?12> ?13>	DNA Homo	sap	oiens	5											
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_	Asp		-				-		_					_	-	·	,,

	_		-		att Ile	_								-	96
					ctc Leu										144
		-	-		tcc Ser		-		-	-	-		_	_	192
					ggc Gly 70										240
_					999 Gly										288
-		-		_	ttt Phe	_	-	 	_	-		_	_		336
					tcc Ser										384
•					tgg Trp	-					-	-		_	432
					cag Gln 150										480
			-		ccc Pro					-					528
				_	gag Glu	_	-			_					576

	-	_		_		-		aag Lys			_			_		624
_			-					agc Ser	_	_		_	-		-	672
-		-	_					aga Arg							_	720
_		-				-		tac Tyr		-	-	_		-		768
			-	-	-			gaa Glu 265	-	-			-	_	_	816
	_		_			•	• •	aag Lys	•	_		_	-	-		864
								acg Thr								912
								ttt Phe								960
			-					atg Met				-				1008
_	_	-	-				-	ttc Phe 345			-				-	1056
-		_					-	att Ile	_	-			-			1104

301

aac tot gac agc aag cag aaa otg aat gac tga 1137 Asn Ser Asp Ser Lys Gln Lys Leu Asn Asp \* 370 375 <210> 212 <211> 378 <212> PRT <213> Homo sapiens <400> 212 Met Asp Leu Ala Gly Leu Leu Lys Ser Gln Phe Leu Cys His Leu Val 5 10 Phe Cys Tyr Val Phe Ile Ala Ser Gly Leu Ile Ile Asn Thr Ile Gln 25 Leu Phe Thr Leu Leu Leu Trp Pro Ile Asn Lys Gln Leu Phe Arg Lys 40 Ile Asn Cys Arg Leu Ser Tyr Cys Ile Ser Ser Gln Leu Val Met Leu 60 55 Leu Glu Trp Trp Ser Gly Thr Glu Cys Thr Ile Phe Thr Asp Pro Arg 70 75 Ala Tyr Leu Lys Tyr Gly Lys Glu Asn Ala Ile Val Val Leu Asn His 90 Lys Phe Glu Ile Asp Phe Leu Cys Gly Trp Ser Leu Ser Glu Arg Phe 105 Gly Leu Leu Gly Gly Ser Lys Val Leu Ala Lys Lys Glu Leu Ala Tyr 120 125 Val Pro Ile Ile Gly Trp Met Trp Tyr Phe Thr Glu Met Val Phe Cys 130 135 140 Ser Arg Lys Trp Glu Gln Asp Arg Lys Thr Val Ala Thr Ser Leu Gln 150 155 His Leu Arg Asp Tyr Pro Glu Lys Tyr Phe Phe Leu Ile His Cys Glu 170 Gly Thr Arg Phe Thr Glu Lys Lys His Glu Ile Ser Met Gln Val Ala 185 Arg Ala Lys Gly Leu Pro Arg Leu Lys His His Leu Leu Pro Arg Thr 200 Lys Gly Phe Ala Ile Thr Val Arg Ser Leu Arg Asn Val Val Ser Ala 215 220 Val Tyr Asp Cys Thr Leu Asn Phe Arg Asn Asn Glu Asn Pro Thr Leu 230 235 Leu Gly Val Leu Asn Gly Lys Lys Tyr His Ala Asp Leu Tyr Val Arg 245 250 255

Arg	Ile	Pro	Leu 260	Glu	Asp	Ile	Pro	G1u 265	Asp	Asp	Asp	Glu	Cys 270	Ser	Ala	
Trp	Leu	His 275	Lys	Leu	Tyr	G1n	G1u 280	Lys	Asp	Ala	Phe	G1n 285	Glu	Glu	Tyr	
Tyr	Arg 290		Ġly	Thr	Phe	Pro 295		Thr	Pro	Met	Val 300		Pro	Arg	Arg	
Pro 305		Thr	Leu	Val	Asn 310	Trp	Leu	Phe	Trp	Ala 315		Leu	Val	Leu	Tyr 320	
Pro	Phe	Phe	Gln	Phe 325	Leu	Val	Ser	Met	Ile 330	Arg	Ser	Gly	Ser	Ser 335	Leu	
Thr	Leu	Ala	Ser 340	Phe	Ile	Leu	Val	Phe 345	Phe	Val	Ala	Ser	Val 350	Gly	Val	
Arg	Trp	Met 355	Ile	Gly	Val	Thr	G1u 360	He	Asp	Lys	Gly	Ser 365	Ala	Tyr	Gly	
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_	_			-	-	Glu					-				-	40
	-	-	-	Ala	Gly	tgc Cys	Ala	Ala	Asp	Gln		Lys	Gln			96
_		-			-	ttc Phe						_				144
						agc Ser 55										192
ссс	agc	aac	acc	cct	gcc	acg	ccg	ССС	aac	ttc	ссс	gat	gcg	ctg	gcc	240

Pro 65		Asn	Thr	Pro	Ala 70	Thr	Pro	Pro	Asn	Phe 75		Asp	Ala	Leu	A1a 80	
					cgc Arg											288
	_		_	-	gcc Ala	_				_			_			336
	-	-		_	ccc Pro								_			384
					cac His				-		-		_			432
					999 Gly 150			-	_		_	-		-	_	480
-	ggc Gly	_	-	tga *												495
	<2 <2	210> 211> 212> 213>	164 PRT	Sap	oiens	;										
		100> Va1		_	Asp	Glu	Leu	Arg		Gln	Val	Met	Ile		Gln	
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Gln	Ala	A1a 35		Trp	Gln	Phe	G1u 40		Ala	Leu	Ser	Thr 45		Phe	G1n	
	50	Asn				55					60	Met			Thr .	
Pro 65	Ser	Asn	Thr	Pro	Ala 70	Thr	Pro	Pro	Asn	Phe 75	Pro	Asp	Ala	Leu	Ala 80	

Met	Phe	Ser	Lys	Leu 85	Arg	Ala	Ser	Glu	Gly 90	Leu	Gln	Ser	Ser	Asn 95	Ser	
Pro	Met	Thr	Ala 100		Ala	Cys	Ser	Pro 105		Ala	Asn	Phe	Ser 110		Phe	
Trp	Ala	Ser 115	Ser	Pro	Pro	Ser	His 120	Gln	Ala	Pro	Trp	Ile 125	Pro	Pro	Ser	
	130					135					140	Pro				
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Asp	Gly	Gln	Arg													
	<2 <2	212>	3105 DNA		oiens	5										
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	_											gat Asp				96
						Leu		Пe				aag Lys 45	Thr			144
		-										ggc Gly				192
		-						_				aag Lys				240
aaa	ggc	aaa	ggt	aaa	aaa	cat	gaa	gca	gat	gag	ttg	agt	gga	gat	gct	288

Lys	Gly	Lys	Gly	Lys 85	Lys	His	Glu	Ala	Asp 90	Glu	Leu	Ser	Gly	Asp 95	Ala	
		_		-	-				-		-			aat Asn		336
	_				-			-	-		-	-		gaa Glu	_	384
		-		_	-	-					_			ctc Leu		432
-	_	-												gga Gly		480
_	_		-			-		-	_	-	_		-	gct Ala 175		528
_		-	_	-					-		٦.			gaa Glu	-	576
_				-		_				-				gaa Glu	-	624
										-			-	cac His		672
													_	gag Glu		720
-							_	-			-			ctg Leu 255	-	768
ttt	gat	ggt	gat	gac	ctc	cta	gaa	aca	ggt	aaa	aat	gtg	aaa	att	aca	816

Phe	Asp	Gly	Asp 260	Asp	Leu	Leu	Glu	Thr 265	Gly	Lys	Asn	Val	Lys 270	Ile	Thr	
					aag Lys											864
_	_		_	-	agc Ser	_	-			_						912
					gac Asp 310											960
			-		aag Lys											1008
	_	•			ccc Pro	-				-				-	_	1056
-			_	-	tct Ser		-									1104
		-			agt Ser		-			-		-				1152
			-	_	gga Gly 390							-	-	-	-	1200
-					aaa Lys		-	_	_	_	-	-		_	_	1248
		-	_	-	cct Pro		-		_				-		-	1296
tct	tca	agc	aca	gag	gtg	tcc	agg	tgt	att	gca	cat	ctt	cat	cgc	act	1344

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Ser	Ser	Ser 435	Thr	Glu	Val	Ser	Arg 440	Cys	Ile	Ala	His	Leu 445	His	Arg	Thr	
														gat Asp		1392
	_		-	_	-		-		-	-	_	-	-	tca Ser	-	1440
-			-									_	-	aca Thr 495		1488
														gaa Glu		1536
	-	-	_	_		-			-			-		aag Lys		1584
-				_										agt Ser		1632
														ata Ile		1680
_					-		_	_			-	-		aga Arg 575		1728
					-	_	_	-	_	-		-	-	cta Leu		1776
			-				_							ttt Phe		1824
aag	atg	aag	gaa	caa	agg	ttg	aga	gaa	cat	tta	gtt	cgt	ttt	gaa	agg	1872

Lys	Met 610	Lys	Glu	Gln	Arg	Leu 615	Arg	Glu	His	Leu	Va1 620	Arg	Phe	Glu	Arg		
_	_	-	-	_	-	ctt Leu	-	-		-			-		-	1	.920
-	_	-		-	Ğlu	cgc Arg					_	-		-	-	1	.968
	-	_		-	_	gag Glu	-						-			2	2016
						atg Met											:064
	_		-	-	_	cgt Arg 695				-						2	112
-	-		-		-	agg Arg			-	_		_		_		2	160
_					_	aaa Lys	_		_	_	_	-			-	2	208
-						gag Glu										2	256
-						tcc Ser	-									2	304
	-		_		-	gag G1u 775										2	352
gta	cag	tct	tca	tct	ttt	gaa	agg	cgg	gat	cgc	ttt	gtt	ggt	caa	agt	2	400

Va1 785	Gln	Ser	Ser	Ser	Phe 790	Glu	Arg	Arg	Asp	Arg 795	Phe	Val	Gly	Gln	Ser 800	
				-	-	cct Pro		-	_		_	_		_		2448
						ttc Phe										2496
						aga Arg										2544
	-	_	_		_	acg Thr 855					_			_		2592
						cga Arg										2640
				-	_	gga Gly	_	-			-			_		2688
						cga Arg										2736
						999 Gly		_	-	_	-	-				2784
						gga G1y 935										2832
				Glu		cga Arg			Val							2880
aca	agc	gga	cca	agg	aaa	gag	tgg	cat	ggt	cca	ccc	tct	caa	<b>ggg</b>	cct	2928

Thr	Ser	Gly	Pro	Arg 965	Lys	Glu	Trp	His	G1y 970	Pro	Pro	Ser	Gln	Gly 975	Pro	
-			_	_		cga Arg	-		_			_		-		2976
_			Gln			agt Ser		Ala					Arg		-	3024
		Ser				atg Met 1019	Pro					Ser				3072
	Phe					ccg Pro )										3105
	. <'a	212>	1034		oiens	5										
Met		400> Ala		Thr	Gly	Ala	Val	Ala	Ala	Ser	Ala	Ala	Ser	Gly	Gln	
1				5	-	Thr			10					15		
		•	20	•			•	25	-			•	30	•		
Glu	Leu	Lys 35	Arg	Arg	Asn	Leu	Asp 40	Ile	Thr	Gly	Val	Lys 45	Thr	Val	Leu	
Пe	Ser 50	Arg	Leu	Lys	Gln	Ala 55	Ile	Glu	Glu	Glu	Gly 60	Gly	Asp	Pro	Asp	
Asn 65		Glu	Leu	Thr	Va1 70	Ser	Thr	Asp	Thr	Pro 75	Asn	Lys	Lys	Pro	Thr 80	
	Gly	Lys	Gly	Lys 85		His	Glu	Ala	Asp 90		Leu	Ser	Gly	Asp 95		
				05			_			^	C1	Lou	61		Gln	
Ser	Val	Glu	-	Asp	Ala	Phe	He		Asp	Cys	GIU	Leu		MSII	um	
			100	•		Phe Gly		105	-				110			

Ala	Glu	Glu	Asn	Lys	Arg	Ala	His	Glu	Leu	Ile	Glu	Ala	Glu	Gly	Пe
145					150					155					160
Glu	Asp	Пe	Glu	Lys	Glu	Asp	Ile	Glu	Ser	Gln	Glu	Пe	Glu	Ala	Gln
				165					170					175	
Glu	Gly	Glu	Asp	Asp	Thr	Phe	Leu	Thr	Ala	Gln	Asp	Gly	Glu	Glu	Glu
•			180					185					190		
Glu	Asn	Glu	Lys	Asp	He	Ala	Gly	Ser	Gly	Asp	Gly	Thr	Gln	Glu	Val
		195					200					205			
Ser	Lys	Pro	Leu	Pro	Ser	Glu	Gly	Ser	Leu	Ala	Glu	Ala	Asp	His	Thr
	210	•				215					220				
Ala	His	Glu	Glu	Met	Glu	Ala	His	Thr	Thr	Val	Lys	Glu	Ala	Glu	Asp
225					230					235					240
Asp	Asn	He	Ser	Val	Thr	Пe	Gln	Ala	Glu	Asp	Ala	IJе	Thr		Asp
				245					250					255	
Phe	Asp	Gly	Asp	Asp	Leu	Leu	Glu		Gly	Lys	Asn	Val		Пe	Thr
			260					265					270		
Asp	Ser		Ala	Ser	Lys	Pro	-	Asp	Gly	Gln	Asp		Ile	Ala	Gln
		275					280					285			
Ser	Pro	Glu	Lys	Glu	Ser	-	Asp	Tyr	Glu	Met		Ala	Asn	His	Lys
	290					295					300				
•	Gly	Lys	Lys	Glu		Cys	Val	Lys	Gly		Pro	Val	Glu	Lys	
305			_	_	310			0.3	_	315			0.3		320
Ala	Arg	Glu	Ser		Lys	Lys	Ala	Glu		Gly	Asp	Lys	Glu		Asp
<b>T</b> I	1.			325	D	C	C = :=	Tl	330	۸٦.	C	C1	03	335	1
ınr	Leu	Lys		ыу	Pro	5er	ser		GIY	АТа	5er	GIY		Ala	Lys
C	C	C	340	61	C =	1	۸	345	مند ا	Thus	C	C	350	۸	۸
ser	Ser		Lys	GIU	5er	Lys		zer.	Lys	mr	zer.		Lys	ASP	ASP
1	Gly	355	The	C02	Con	Thn	360	Clv	Can.	con	C14	365	Con	The	Lvc
Lys	-	Ser	HOIL	261	Sei	375	361	uly	261	361	380	361	361	1111	Lys
۸cn	370 Ile	Trn	V-3	San	Gly		Son	Sor	Acn	Thr		۸la	۸٦۵	۸cn	Lou
385	116	пр	vai	361	390	Leu	361	361	ДЗП	395	Lys	Ala	Ala	Tah	400
	Asn	Lou	Dho	GIV		Tyr	GIV	Lvc	Val		Sar	د ۱۸	Lvc	۷al	
Lys	MOII	Leu	rne	405	Lys	1 9 1	uly	Lys	410	LCU	361	Ala	Lys	415	vai
Thr	Asn	د [ Δ	Ara		Dro	Glv	Δla	Lvc		Tvr	Glv	פוז	Val		Mot
1111	A311	Aia	420	361	110	uiy	Aiu	425	Cys	131	uiy	110	430	1111	TICL
Sar	Ser	Sar		Glu	Val	Ser	Δra		Πρ	Δla	Hic	Leu		Δra	Thr
201	JCI	435	1111	uiu	Vui	301	440	Cy 3	110	Aiu	1113	445	1113	Ai 9	1111
Glu	Leu		Glv	Gln	يرم ا	פוז		Val	Glu	Lvc	Val		G1v	Δsn	Pro
uiu	450	1113	uij	4111	LCG	455	501	· u ·	aru		460		uij	, .sp	
Ser	Lys	Lvc	Glu	Met	Lvc		Glu	Δsn	Δsn	Glu		Ser	Ser	Ser	Δra
465	LJ 3	<i>- J J</i>	ulu	1100	470	_,,	uiu	,,511	, wp	475	_,,	٠.	JC1	JC1	480
	Ser	Glv	Asn	l vc		Asn	Thr	Ser	Asn		Ser	Ser	۱vs	Thr	
50,	501	₩ 1 <i>3</i>	, .JP	485	LJ J	7 1011		501	490	, a	501	551	-53	495	J.111
									, , ,						

Ala	Ser	Val	Lys 500	Lys	Glu	Glu	Lys	Arg 505	Ser	Ser	Glu	Lys	Ser 510	Glu	Lys
Lys	Glu	Ser 515	Lys	Asp	Thr	Lys	Lys 520	Ile	Glu	Gly	Lys	Asp 525	Glu	Lys	Asr
•	530					535			Glu		540				
G1u 545	Lys	Lys	Arg	Ile	Ser 550	Ser	Lys	Ser	Pro	Gly 555	His	Met	Val	Пe	Leu 560
Asp	Gln	Thr	Lys	G1y 565	Asp	His	Cys	Arg	Pro 570	Ser	Arg	Arg	Gly	Arg 575	Tyr
	-		580					585	Lys				590		
Lys	Lys	Arg 595	Asp	L <sub>.</sub> ys	Asp	Tyr	Arg 600	Arg	Lys	Glu	Ile	Leu 605	Pro	Phe	Glu
•	610			•	•	615			His		620	_			
625	•	•			630				Arg	635					640
	_			645					Ile 650					655	
Arg	Glu	Arg	Leu 660	Gln	Arg	Glu	Arg	G1u 665	Arg	Leu	Glu	Пe	G1u 670	Arg	Glr
Lys	Leu	G1u 675	Arg	G1u	Arg	Met	G1u 680	Arg	Glu	Arg	Leu	G1u 685	Arg	Glu	Arg
Ιle	Arg 690	Ile	G1u	Gln	Glu	Arg 695	Arg	Lys	Glu	Ala	G1u 700	Arg	Ile	Ala	Arg
G1u 705	Arg	Glu	Glu	Leu	Arg 710	Arg	Gln	Gln	Gln	G1n 715	Leu	Arg	Tyr	Glu	G1r 720
Glu	Lys	Arg	Asn	Ser 725	Leu	Lys	Arg	Pro	Arg 730	Asp	Val	Asp	His	Arg 735	Arg
Asp	Asp	Pro	Tyr 740	Trp	Ser	Glu	Asn	Lys 745	Lys	Leu	Ser	Leu	Asp 750	Thr	Asp
Ąla	Arg	Phe 755	Gly	His	Gly		Asp 760	-	Ser	Arg	G1n	G1n 765	Asn	Arg	Phe
Asn	Asp 770	Phe	Asp	His	Arg	G1u 775	Arg	Gly	Arg	Phe	Pro 780	Glu	Ser	Ser	Ala
Va1 785	Gln	Ser	Ser	Ser	Phe 790	Glu	Arg	Arg	Asp	Arg 795	Phe	Val	Gly	Gln	Ser 800
Glu	Gly	Lys	Lys	A1a 805	Arg	Pro	Thr	Ala	Arg 810	Arg	Glu	Asp	Pro	Ser 815	Phe
Glu	Arg	Tyr	Pro 820	Lys	Asn	Phe	Ser	Asp 825	Ser	Arg	Arg	Asn	G1u 830	Pro	Pro
Pro	Pro	Arg 835	Asn	Glu	Leu	Arg	G1u 840	Ser	Asp	Arg	Arg	G1u 845	Val	Arg	Gly

Glu	850	Asp	Glu	Arg	Arg	1nr 855	vai	Пе	He	HIS	860	Arg	Pro	Asp	He	
Thr 865	His	Pro	Arg	His	Pro 870	Arg	Glu	Ala	Gly	Pro 875	Asn	Pro	Ser	Arg	Pro 880	
	Ser	Trp	Lys	Ser 885		Gly	Ser	Met	Ser 890		Asp	Lys	Arg	G1u 895		
Arg	۷al	Glu	Arg 900		Glu	Arg	Ser	G1y 905		Glu	Val	Ser	Gly 910		Ser	
Val	Arg	Gly 915		Pro	Pro	Gly	Asn 920		Ser	Ser	Ala	Ser 925		Tyr	Gly	
Ser	Arg 930		Gly	Asp	Arg	Gly 935		Пe	Thr	Asp	Arg 940		Gly	Gly	Ser	
G1n 945		Tyr	Pro	Glu	G1u 950	Arg	His	Val	Val	G1u 955		His	Gly	Arg	Asp 960	
	Ser	Gly	Pro	Arg 965		Glu	Trp	His	Gly 970		Pro	Ser	G1n	G1y 975		
Ser	Tyr	His	Asp 980		Arg	Arg	Met	G1y 985		G1y	Arg	Ala	G1y 990		Gly	
Met	Пе	Thr 995		His	Ser	Ser	Asn 1000	Ala	Ser	Pro	Ile	Asn 1005	Arg	Пе	Val	
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			_	-		cgg Arg	-		-	_			-	-	_	96
gag	agt	gca	ссс	cag	agg	gtt	cta	ttg	ссс	aca	caa	aaa	ata	gac	aat	144

Glu	Ser	A1 a 35	Pro	Gln	Arg	Val	Leu 40	Leu	Pro	Thr	Gln	Lys 45	Ile	Asp	Asn	
_	_		-	•	-	cag Gln 55		_			-			-	•	192
_		-		-	_	cac His			-							240
				-		ttc Phe	_							_		288
						cca Pro										336
_						gag Glu										384
_		-				cga Arg 135	_	-		-		-		-	-	432
-		-	-	-		gac Asp			-		_					480
-	-				_	gcc Ala		_	-			-				528
-	-		_			gag Glu		-	_							576
~ ~	•	•	-	_		gat Asp	•		_	-		-		-		624
cta	ttg	tca	gat	gaa	gac	tgt	atg	tct	gtg	ссс	gga	aaa	act	cac	aga	672

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Leu	Leu 210	Ser	Asp	Glu	Asp	Cys 215	Met	Ser	Val	Pro	Gly 220	Lys	Thr	His	Arg	
~		•	_		•			_	-	_		•	•	cgc Arg		720
-			_	_							_		_	cag G1n 255	_	768
			-					_						gat Asp	-	816
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	_	-		-			-	_	_		-			aaa Lys		912
-	-			_	-						-		_	gag Glu	_	960
	-	-		_									-	gaa Glu 335	_	1008
		_	_		•	-	_		-	•		_	_	gaa Glu		1056
	-													atc Ile		1104
Tyr			-					-						gga Gly		1152
cct	ctc	aat	gtc	tta	cca	aag	aaa	gga	ctc	aca	gca	aag	caa	act	gaa	1200

Pro . 385	Leu	Asn	Va1	Leu	Pro 390	Lys	Lys	Gly	Leu	Thr 395	Ala	Lys	Gln	Thr	Glu 400	
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	_					agc Ser							-	-		1296
						aag Lys						_				1344
		_			•	gag Glu 455		_			-		-	_	-	1392
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Glu	Ser	A1a 35	Pro	Gln	Arg	Val	Leu 40	Leu	Pro	Thr	Gln	Lys 45	Ile	Asp	Asn	
Glu	Glu 50	Arg	Arg	Ala	Glu	G1n 55	Arg	Lys	Tyr	Gly	Val 60	Phe	Phe	Asp	Asp	
Asp 65		Asp	Tyr	Leu	G1n 70	His	Leu	Lys	Glu	Pro 75		Gly	Pro	Ser	Glu 80	
	Пе	Pro	Ser	Ser 85		Phe	Ser	Ala	His 90		Arg	Arg	Glu	G1u 95		
Glu	Glu	Thr	Leu		Пe	Pro	Ser	Thr 105		Ile	Lys	Leu	Pro		Ser	

	Phe	Ala 115	Ser	Glu	Phe	Glu	Glu 120	Asp	Val	Gly	Leu	Leu 125	Asn	Lys	Ala
Ala	Pro 130	Val	Ser	Gly	Pro	Arg 135	Leu	Asp	Phe	Asp	Pro 140	Asp	Ile	Val	Ala
145					150	·				155				Leu	160
,	·			165				-	170		-			G1u 175	_
	·		180	·				185	·	·			190	Glu	•
	·	195		•		·	200		·			205		Ala	-
	210		•		·	215					220			His	_
225			·		230					235				Arg	240
		-		245					250	_	_			G1n 255	
			260					265		-			270	Asp	·
•		275	-			·	280					285		Ile	
	290					295					300			Lys	
Lys 305	Ala	Glu	Asn	Cys		Lys	Leu	Asn	Thr	Leu 315	Glu	Pro	Leu	Glu	Asp 320
					310										
	·			325	Asn			·	330	Ser				G1u 335	Met
Ile	Thr	Val	Val 340	325 Leu	Asn Glu	Glu	Ala	Lys 345	330 G1u	Ser Lys	Trp	Asp	Cys 350	335 G1u	Met Ser
Ile Ile	Thr Cys	Val Ser 355	Val 340 Thr	325 Leu Tyr	Asn Glu Ser	Glu Asn	Ala Leu 360	Lys 345 Tyr	330 Glu Asn	Ser Lys His	Trp Pro	Asp Gln 365	Cys 350 Leu	335 Glu Ile	Met Ser Lys
Ile Ile Tyr	Thr Cys Gln 370	Val Ser 355 Pro	Val 340 Thr	325 Leu Tyr Pro	Asn Glu Ser Lys	Glu Asn Gln 375	Ala Leu 360 Ile	Lys 345 Tyr Arg	330 Glu Asn Ile	Ser Lys His Ser	Trp Pro Ser 380	Asp Gln 365 Lys	Cys 350 Leu Thr	335 Glu Ile Gly	Met Ser Lys Ile
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Ile Ile Tyr Pro 385 Arg	Thr Cys Gln 370 Leu	Val Ser 355 Pro Asn Gln	Val 340 Thr Lys Val	325 Leu Tyr Pro Leu Ile 405	Asn Glu Ser Lys Pro 390 Asn	Glu Asn Gln 375 Lys Gly	Ala Leu 360 Ile Lys Ser	Lys 345 Tyr Arg Gly Asp	330 Glu Asn Ile Leu Leu 410	Ser Lys His Ser Thr 395 Pro	Trp Pro Ser 380 Ala Lys	Asp Gln 365 Lys Lys Val	Cys 350 Leu Thr Gln Ser	335 Glu Ile Gly Thr Thr 415	Met Ser Lys Ile Glu 400 Gln
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Ile Ile Tyr Pro 385 Arg Pro Ala	Thr Cys Gln 370 Leu Ile Arg	Val Ser 355 Pro Asn Gln Ser Lys 435	Val 340 Thr Lys Val Met Lys 420 Glu	325 Leu Tyr Pro Leu Ile 405 Asn Glu	Asn Glu Ser Lys Pro 390 Asn Glu Arg	Glu Asn Gln 375 Lys Gly Ser Lys	Ala Leu 360 Ile Lys Ser Lys Glu 440	Lys 345 Tyr Arg Gly Asp Glu 425 Arg	330 Glu Asn Ile Leu 410 Asp	Lys His Ser Thr 395 Pro Lys Val	Trp Pro Ser 380 Ala Lys Arg Glu	Asp Gln 365 Lys Lys Val Ala Lys 445	Cys 350 Leu Thr Gln Ser Arg 430 Lys	335 Glu Ile Gly Thr Thr 415	Met Ser Lys Ile Glu 400 Gln Gln Asn

318

Asn 465	Leu	Lys	Lys	Asn	Va1 470	Glu	Gly	Leu	Lys	Leu 475						
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						gga Gly							-		-	144
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 Val Lys
 Leu Glu Pro Asp Gly Leu Leu Val Trp Val Leu Ala Gly Ala 35

 Leu Gly Leu Ser Leu Val Phe Ser Leu Val Ser Val Pro Leu Gln Cys 50

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Ile Pro Val Thr Tyr Val Phe Asn His Leu Ala Ala Gln His Asp Ser
20 25 30

tgg act att gta ggg gtt gct gcc ctc atc ctg ttc ctg gta gca ctg
Trp Thr Ile Val Gly Val Ala Ala Leu Ile Leu Phe Leu Val Ala Leu
35 40 45

ctg gct cgt gtc ctc gtc aaa aga aaa cca ccc cgg gac cca ctg ttc
Leu Ala Arg Val Leu Val Lys Arg Lys Pro Pro Arg Asp Pro Leu Phe
50 55 60

			_			_						aac Asn				240
	_			_				_			-	aca Thr			_	288
•	-		•	_		_			-			cac His	-		-	336
		-			-			-	-			gtg Val 125		_	-	 384
												cta Leu				432
				_	-	-	-	-				gga Gly			-	480
	-				_		-		-			tta Leu	-			528
		_			-		-			-		tat Tyr		_		576
												gaa Glu 205				624
		-										gtt Val				672
	-	_					_		-			att Ile		_	-	720

_			_		_	cga Arg		-				-			768
	-	_		-	-	tat Tyr			_	_	_	-	Tyr	•	816
						ttt Phe									864
		_				cct Pro 295	-		-			_			912
-	-	_	_	_		tct Ser			_				•	_	960
						gtc Val									1008
-				-		gga Gly	-		_		~	-		•	1056
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Trp	Thr	Ile 35	Val	Gly	Val	Ala	Ala 40	Leu	Пe	Leu	Phe	Leu 45	Val	Ala	Leu
Leu	A1a 50	Arg	Val	Leu	Val	Lys 55	Arg	Lys	Pro	Pro	Arg 60	Asp	Pro	Leu	Phe
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			100		Tyr			105			_		110		-
		115			Ala		120					125			
	130		·		Glu	135	·	·			140		·		
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				165	Arg		-		170					175	
			180		Val			185				-	190		
		195	-		Tyr		200	•				205			
	210				Arg	215		·			220			•	
225					Phe 230				-	235					240
				245	Cys				250					255	
Leu	Lys	Asp	Pro 260	Ala	Ala	Tyr	Pro	Lys 265	Ile	Gln	Met	Leu	A1 a 270	Tyr	Met
		275			Tyr		280				Ť	285			
	290				Met	295	•				300			•	-
Leu 305	Ala	Gln	Ala	Gln	Phe 310	Ser	His	He	Gly	Ala 315	Ser	Leu	His	Ala	Arg 320
				325	Arg				330		-			335	
Ąla	Leu	Asn	Ile 340	Ala	Tyr	Gly	Val	Leu 345	Pro	Gln	Leu	Leu	Ala 350	Tyr	Arg

Cys	Ile	Tyr 355	Lys	Pro	Gļu	Phe	Phe 360	Ile	Lys	Thr	Lys	Ala 365	Glu	Glu	Lys	
Val	G1u 370															
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						atc Ile										96
	9,0		20					25			,		30	5	1.0	
	-	-	_			gaa Glu									_	144
•	'	35					40		J			45	J			
_						cac His	-						-		_	192
	50					55					60				•	
_		-		-	-	aag Lys			_					_		240
65					70					75					80	
						ttt Phe										288
				85					90					95		
						gtc Val										336
			100					105					110			
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Leu Thr Leu Ile Lys Gln His Gln Glu Leu Ile Leu Glu Ala Thr Ser
                        55
                                            60
Val Pro Asp Ile Cys Asp Lys Phe Lys Gln Ile Thr Lys Gly Ser Phe
                                        75
Val Met Glu Cys His Thr Phe Met Gln Lys Ile Phe Ser Glu Pro Gly
                                    90
Ser Leu Ser Met Ala Thr Val Ala Lys Leu Arg Glu Ser Cys Arg Ala
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                                                    110
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tgg gcc tcc gtg agc gcc cag acc gat gcc acc ccg gcg gtg acg aca
                                                                       96
Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
            20
                                 25
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					gag Glu		_	_	-						144
_	_				ggg Gly 55				_						192
					gtc Val	-	-	-	-	-		•	•	•	240
-			_	_	tgt Cys	-			_	_	-	-		_	288
-	-		-		agt Ser	-			-	_		_		-	336
-	-		-	-	ttt Phe	-	-			-	-				384
			-		cca Pro 135				-		-		-	-	432
_					ttc Phe	_									480
					cca Pro	-	_		-	_				-	528
					gat Asp						-	-			576
					ctg Leu										624

				-	_	act Thr 215			_	-				_	672
					_	tgc Cys		-			-			-	720
		_	-	-	-	tgc Cys		_				-	_	•	768
						agc Ser									816
_		-		_		aga Arg		_	-			-	_		864
	_		_			aat Asn 295		-		-			-		912
_		-		-		ctc Leu	_		-			•		-	960
			-		-	gta Val	_		_				-	-	1008
						gat Asp									1056
						cag Gln									1104
-			-		-	cct Pro 375		-					-		1152

											aag Lys					1200
											att Ile					1248
											cgg Arg					1296
											aga Arg					1344
											agc Ser 460					1392
											aat Asn					1440
											acc Thr					1488
											gtt Val					1536
tgg Trp	act Thr	aaa Lys 515	tac Tyr	gga Gly	tcc Ser	ctg Leu	ctg Leu 520	aat Asn	cca Pro	cag Gln	gcc Ala	aaa Lys 525	ata Ile	gtc Val	aat Asn	1584
											gag G1u 540					1632
											act Thr					1680

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Ser 225	Leu	Thr	Ser	Ser	Leu 230	Cys	Thr	Asp	Asn	Asn 235	Pro	Ala	Ala	Phe	Leu 240
Val	Asn	Gln	Ala	Val 245	Lys	Cys	Thr	Arg	Lys 250	Ile	Asn	Leu	Glu	G1n 255	Cys
Glu	Glu	Ile	G1u 260	Ala	Leu	Ser	Met	Ala 265	Phe	Tyr	Ser	Ser	Pro 270	Glu	Ile
Leu	Arg	Va1 275	Pro	Asp	Ser	Arg	Lys 280	Lys	Val	Pro	Ile	Thr 285	Val	Gln	Ser
Ile	290		Gln	•		295					300				
Asp 305	Val	Leu	Gln	Pro	Thr 310	Leu	Val	Asn	Ala	Gly 315	His	Phe	Ser	Leu	Cys 320
			Val	325			-		330					335	
•			Thr 340					345					350		
		355	Val				360					365			
	370		Gln			375					380				
385		•	Leu		390					395					400
			Thr	405				•	410					415	
Thr	Glu	Gln	Asp 420	Cys	Leu	Ala	Leu	G1u 425	Gly	Val	Arg	Thr	Pro 430	Val	Leu
Phe	Gly	Tyr 435	Thr	Met	Gln	Ser	G1y 440	Cys	Lys	Leu	Arg	Leu 445	Thr	Gly	Ala
	450	•	Gln			455					460				
G1n 465	Gly	Phe	Pro	Asp	Tyr 470	Val	Ala	Pro	Phe	Gly 475	Asn	Ser	Gln	Ala	G1n 480
Asp	Met	Leu	Asp								Thr		Ser	Phe 495	Asn
Arg	Lys	Asp	Ser 500	Cys	Gln	Leu	Pro	G1y 505	Ala	Leu	Val	Ile	G1u 510	Val	Lys
Trp	Thr	Lys 515	Tyr	Gly	Ser	Leu	Leu 520	Asn	Pro	Gln	Ala	Lys 525	Ile	Val	Asn
۷a۱	Thr 530	Ala	Asn	Leu	He	Ser 535	Ser	Ser	Phe	Pro	G1u 540	Ala	Asn	Ser	Gly
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	ctg Leu												144
	cgc Arg 50												192
	gac Asp												240
	cag G1n												288
	cgg Arg												336
	aat Asn												384

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				atg Met	Tyr					5	28
				tgc Cys						5	76
				ttc Phe						6	24
				agc Ser 215						6	72
_	 -		-	att Ile						7.	20
				cag Gln						7	68
				ctg Leu					ctt Leu `	8	16
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				cac His 295						9	12

-	agc Ser	•		-	•	_	_				-			-	-	50 53
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Val	Leu	G1n 35		Glu	Glu	Gln	Asn 40	Cys	Ser	Gly	Gly	A1a 45	Leu	Asn	His	
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Arg 65	Asp	Asp	Cys	Lys	Tyr 70	Glu	Cys	Met	Trp	Va1 75	Thr	Val	Gly	Leu	Tyr 80	
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Ser	Arg	Phe	Leu 100	Phe	Phe	Gln	Glu	Pro 105	Ala	Ser	Ala	Val	Ala 110		Phe	
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Thr	Asp	Leu	Thr	Glu 165	Lys	Met	Asp	Tyr	Phe 170	Cys	Ala	Ser	Thr	Val 175	Ile	
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Pro	Ala	Val 195		Ser	Ala	Phe	Arg 200		Leu	Leu	Leu	Leu 205		Leu	Thr	
Val	His 210		Ser	Tyr	Leu	Ser 215		Ile	Arg	Phe	Asp 220		Gly	Tyr	Asn	

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Leu 65	Gln	Leu	Leu	Gly	Arg 70	Leu	Pro	Leu	Phe	Gly 75	Leu	Gly	Arg	Leu	Va1 80	
_	_	_			-	tgg Trp	-		_		-	-			-	288
	_		-			gac Asp				_		_	-			336
_	-				-	acc Thr				-			-			384
						atg Met 135										432
		-		-		acc Thr			-	-		_	-	-	-	480
_	-			_		ccg Pro					-	_			-	528
_	-				-	gac Asp				-			_			576
_				_		gaa Glu			_			_		_	_	624
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<213> Homo sapiens

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Leu Tyr Ala Val Asp Tyr Glu Thr Leu Thr Arg Pro Phe Ser Gly Arg
                            40
Arg Leu Pro Val Arg Ala Trp Ala Asp Val Arg Arg Glu Xaa Arg Leu
Leu Gln Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
                    70
                                        75
Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
                                    90
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
                                105
Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
Arg Glu Ile Glu His Val Met Tyr His Asp Trp Arg Leu Val Pro Lys
                        135
                                            140
His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
                    150
                                        155
Leu Ala Ser Val Pro Tyr Pro Pro Leu Leu Arg Ala Met Ile Ile Ala
                                    170
                165
Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
                                185
Val Gln Arg Ile Arg Met Glu Pro Trp Asp Tyr Pro Ala Lys Gln Glu
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                                                205
Asp Lys Gly Arg Ala Lys Gly Thr Pro Val
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                        215
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     <222> (1)...(1116)
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336

<221> misc feature

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145					150					155					160	
					aat Asn										-	528
					cct Pro											576
-		-		_	cct Pro		-	-	-							624
-		-			acc Thr		-	-			-					672
_					gag Glu 230	_				-	_	-		_		720
	-	-			aag Lys	-										768
	_	_	_		agt Ser				_		_			-	-	816
					ttc Phe											864
					gac Asp	-	-			_	_		_		-	912
					ggc Gly 310		_				_	_		_		960
					cgg Arg											1008

338

325 330 335 cag gag gag agc gcc gag cgg agn agg ccc tca cag cat gtg gtg ctc 1056 Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu 340 345 ago ctg act ttc aag cgt tat gtc ttc gac acc cac aag cgc atg gtt 1104 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 360 365 cag tct ccc tga 1116 Gln Ser Pro \* 370 <210> 232 <211> 371 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1) ... (371) <223> Xaa = Any Amino Acid <400> 232 Met Ser Val Ala His Cys Phe Ser Ile Lys Gly Gln Gly Thr Val Met 10 Thr Gly Thr Ile Leu Ser Gly Ser Ile Ser Leu Gly Asp Ser Val Glu 25 Ile Pro Ala Leu Lys Val Val Lys Lys Val Lys Ser Met Gln Met Phe 40 His Met Pro Ile Thr Ser Ala Met Gln Gly Asp Arg Leu Gly Ile Cys 55 Val Thr Gln Phe Asp Pro Lys Leu Leu Glu Arg Gly Leu Val Cys Ala 70 Pro Glu Ser Leu His Thr Val His Ala Ala Leu Ile Ser Val Glu Lys Ile Pro Tyr Phe Arg Gly Pro Leu Gln Thr Lys Ala Lys Phe His Ile 105 Thr Val Gly His Glu Thr Val Met Gly Arg Leu Met Phe Phe Ser Pro 120 Ala Pro Asp Asn Phe Asp Gln Glu Pro Ile Leu Asp Ser Phe Asn Phe 130 135 140

Ser Gln Glu Tyr Leu Phe Gln Glu Gln Tyr Leu Ser Lys Asp Leu Thr 150 155 Pro Ala Val Thr Asp Asn Asp Glu Ala Asp Lys Lys Ala Gly Gln Ala 165 170 Thr Glu Gly His Cys Pro Arg Gln Gln Trp Ala Leu Val Glu Phe Glu 180 185 Lys Pro Val Thr Cys Pro Arg Leu Cys Leu Val Ile Gly Ser Arg Leu 200 205 Asp Ala Asp Ile His Thr Asn Thr Cys Arg Leu Ala Phe His Gly Ile 215 220 Leu Leu His Gly Leu Glu Asp Arg Asn Tyr Ala Asp Ser Phe Leu Pro 230 235 Arg Leu Lys Val Tyr Lys Leu Lys His Lys His Gly Leu Val Glu Arg 245 250 Ala Met Asp Asp Tyr Ser Val Ile Gly Arg Ser Leu Phe Lys Lys Glu 265 Thr Asn Ile Gln Leu Phe Val Gly Leu Lys Val His Leu Ser Thr Gly 280 Glu Leu Gly Ile Ile Asp Ser Ala Phe Gly Gln Ser Gly Lys Phe Lys 295 Ile His Ile Pro Gly Gly Leu Ser Pro Glu Ser Lys Lys Ile Leu Thr 310 315 320 Pro Ala Leu Lys Lys Arg Ala Arg Ala Gly Arg Gly Glu Ala Thr Arg 330 Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu 345 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 . 360 365 Gln Ser Pro 370 <210> 233 <211> 1275 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1275) <221> misc feature <222> (1)...(1275) <223> n = A,T,C or G

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_				-	-	_	_		-	acc Thr	_		-			96
		-	-	-				-	-	ggc Gly		-	_			144
			_	-	_					gga Gly		_	-	-		192
										ggt Gly 75						240
		-						_		tat Tyr						288
_			_							att Ile						336
_	_	-	_							gcc Ala						384
		-				_	_		-	aaa Lys	_			-	-	432
_	-							•		aat Asn 155		-	-			480
_		-						_	_	gag Glu						528

		-						-	gca Ala			_	_			576
-				-					gga G1y						aaa Lys .	624
						-	_		tgt Cys		-					672
	_	-		_			_		atc Ile				-	-		720
-					-			-	aga Arg 250				-			768
	_								gga Gly	_	-		-	_	_	816
-					_		-		acc Thr	-				-		864
_			-	-					gcc Ala	_				_	cca Pro	912
		_		_			_		att Ile	-	_	_			-	960
									ttt Phe 330							1008
						-			gga Gly	-					-	1056

att cct cgg Ile Pro Arg 355	Leu Asn		-	Cys	-	-			-		-	1104
tta gct ttt Leu Ala Phe 370		_	g Lys						-	_		1152
ttg cct cca Leu Pro Pro 385										-	-	1200
ctg gca gaa Leu Ala Glu	_	Lys Ar										1248
gga ggc aag Gly Gly Lys	_			_								1275
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1 Ala Val Ala	5 Thr Ala	-		Asn	10				Gln	15		
Gly Pro Arg	20 Ala Ser	Val Th		25 Asp	Ser	Gly	Pro		30 Leu	۷al	Ser	
35 Ile Ala Gly 50	Thr Arg	Pro Ser	40 - Val	Arg	Asn	Gly	G]n 60	45 Leu	Leu	Val	Ser	
Thr Gly Leu	Pro Ala		G]n	Leu	Leu	Gly 75		Gly	Leu	Ala	Va1 80	
Gly Thr Val	Leu Leu		ı Glu	Asp	Lys		Asn	Пe	Tyr	Ser		

				85					90					95	
Leu	Leu	Phe	Lys 100	Tyr	Phe	Leu	Ala	Glu 105	Gly	Пe	۷al	Asn	Gly 110	His	Thr
Leu	Leu	Val 115		Ser	Ala	Lys	Glu 120		Pro	Ala	Asn	Ile 125		Gln	Glu
Leu	Pro 130		Pro	Leu	Leu	Asp 135		Lys	Cys	Lys	Lys 140	Glu	Phe	Asp	Glu
Asp 145		Tyr	Asn	His	Lys 150		Pro	Glu	Ser	Asn 155		Lys	Met	Lys	Ile 160
	Trp	Arg	Tyr	Gln 165		Leu	Pro	Lys	Met 170		Ile	Gly	Pro	Val 175	
Ser	Ser	Arg	Phe 180		His	Tyr	Tyr	Asp 185		Ser	Lys	Arg	Met 190		Gln
Glu	Leu	Ile 195		Ala	Ser	Asn	Trp 200		Gly	Phe	Phe	Leu 205		Glu	Lys
Ile	Ser 210		Thr	Leu	Lys	Val 215		Pro	Cys	Ser	Leu 220	Thr	Pro	Gly	Tyr
Thr 225		Leu	Leu	Gln	Phe 230		Gln	Asn	Ile	Ile 235	Tyr	Glu	Glu	Gly	Phe 240
Asp	Gly	Ser	Asn	Pro 245	Gln	Lys	Lys	Gln	Arg 250	Asn	Ile	Leu	Arg	Ile 255	Gly
Ile	Gln	Asn	Leu 260	Gly	Ser	Pro	Leu	Trp 265	Gly	Asp	Asp	Ile	Cys 270	Cys	Ala
Glu	Asn	G1y 275	Gly	Asn	Ser	His	Ser 280	Leu	Thr	Lys	Phe	Leu 285	Tyr	Val	Leu
Arg	G1y 290	Leu	Leu	Arg	Thr	Ser 295	Leu	Ser	Ala	Cys	Ile 300	Ile	Thr	Met	Pro
Thr 305	His	Leu	Ile	Gln	Asn 310	Lys	Ala	Ile	Ile	Ala 315	Arg	Val	Thr	Thr	Leu 320
Ser	Asp	Val	Val	Val 325	Gly	Leu	Glu	Ser	Phe 330	Ile	Gly	Ser	Glu	Arg 335	Glu
Thr	Asn	Pro	Leu 340	Tyr	Lys	Asp	Tyr	His 345	Gly	Leu	Ile	His	Ile 350	Arg	Gln
Ile	Pro	Arg 355	Leu	Asn	Asn	Leu	Ile 360	Cys	Asp	Glu	Ser	Asp 365	Val	Lys	Asp
Leu	A1a 370	Phe	Lys	Leu	Lys	Arg 375	Lys	Leu	Phe	Thr	Ile 380	Glu	Arg	Leu	His
Leu 385	Pro	Pro	Asp	Leu	Ser 390	Asp	Thr	Val	Ser	Arg 395	Ser	Ser	Lys	Met	Asp 400
Leu	Ala	Glu	Ser	A1a 405	Lys	Arg	Leu	Gly	Pro 410	Gly	Cys	Gly	Met	Met 415	
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			agc tac gtg Ser Tyr Val	-	
-			gag gag cag Glu Glu Gln 60		
			cag cgg ccc Gln Arg Pro 75	-	
			ggc tgt ggc Gly Cys Gly 90		-
	-		acc aaa ctt Thr Lys Leu		
•		•	tcc acc ctg Ser Thr Leu		
•	_		gat gtg gca Asp Val Ala	_	

	130					135					140				
	-	_			_	ctc Leu									480
_					-	cag Gln									528
	_	-		_		aag Lys	-	-	-					_	576
-	-	_	-	-	-	ttg Leu	_								624
			_	_		cgg Arg 215							-		672
	-	_	_			cag Gln		_					_	 	720
	_		-	_	_	gtc Val				_				 -	768
	•					ctg Leu		-		-			-	 -	816
	-		-			gcc Ala			_			-			864
	_	•	_		•	ttc Phe 295	•		_			_		•	912
	_					gca Ala					_		-	-	960

305			310					315				• .	320	
cgg aag cgc Arg Lys Arg	Phe S		-	_	_			_			-	-	-	1008
gag ctg gcc Glu Leu Ala			_	_					_			_		1056
gcc cag gca Ala Gln Ala 355	Ala A		-					-		-	-		_	1104
cca tct gct Pro Ser Ala 370	_							-					-	1152
aca agt cct Thr Ser Pro 385		Lys												1188
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		115					120					125			
Met	Ala 130	Asp	Leu	Leu	Gln	Gln 135	Gly	Pro	Asp	Val	Ala 140	Pro	Ser	Phe	Leu
Asn 145		Va1	Leu	Asn	Gln 150	Leu	Asn	Trp	Ala	Phe 155	Ser	Glu	Phe	Ile	Gly 160
	Ile	Gln	Glu	Ile 165		Gln	Ala	Ala	Glu 170		Leu	Glu	Arg	Asn 175	
Val	Asp	Ser	Arg 180		Leu	Lys	۷a۱	Cys 185		Thr	Cys	Phe	Asp 190	Leu	Ser
Val	Ser	Leu 195		_	Val	Leu	G1u 200		Thr	Пе	Thr	Leu 205		Pro	Glu
Пе	Phe 210				Thr	Arg 215		Thr	Ser	Glu	Met 220		Leu	Arg	Arg
Leu 225		Gln	Leu	Leu	Asn 230		۷a۱	Leu	Asn	Arg 235		Thr	Ala	Glu	Arg 240
	Leu	Phe	Asp	Arg 245		Val	Thr	Leu	Arg 250		Pro	Gly	Leu	G1u 255	
Val	Asp	His	Tyr 260		Пe	Leu	Val	Ala 265		Thr	Gly	Ile	Leu 270	Val	Gln
Leu	Leu	Val 275		Gly	Pro	Ala	Ser 280		Arg	Glu	Gln	A1 a 285		Ser	۷a۱
Leu	Leu 290	Ala	Asp	Pro	Cys	Phe 295	Gln	Leu	Arg	Ser	Ile 300	Cys	Tyr	Leu	Leu
Gly 305	Gln	Pro	Glu	Pro	Pro 310	Ala	Pro	Gly	Thr	Ala 315	Leu	Pro	Ala	Pro	Asp 320
Arg	Lys	Arg	Phe	Ser 325	Leu	Gln	Ser	Tyr	Ala 330	Asp	Tyr	IJе	Ser	Ala 335	Asp
Glu	Leu	Ala	G1n 340	Val	Glu	Gln	Met	Leu 345	Ala	His	Leu	Thr	Ser 350	Ala	Ser
Ala	Gln	A1 a 355	Ala	Ala	Ala	Ser	Leu 360	Pro	Thr	Ser	Glu	G1u 365	Asp	Ser	Ala
	370					375				-	Ser 380	Ser	Pro	Val	Ala
Thr 385	Ser	Pro	Ala	Lys	Pro 390	Val	Ser	Thr	Ser	Thr 395					
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<221> misc feature

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cag aat att att aag act ctt agg gtt cct ctc agt ttg aag tat tcc Gln Asn Ile Ile Lys Thr Leu Arg Val Pro Leu Ser Leu Lys Tyr Ser

145				150				155					160	
		-	_				_	-		tct Ser			_	528
-					-	-		-		gct Ala				576
	-	_	_		-		-			ttt Phe 205	-	_		624
						-				att Ile				672
										ctt Leu				720
										ttt Phe				768
										cag Gln				816
							-	-		gaa G1u 285				864
					_				-	aat Asn		-		912
						-	-	-		tca Ser				960
										gat Asp				1008

325 330 335 agt ggt aaa tgc cct ctt cca agg caa caa gta aca gaa att ata ttt 1056 Ser Gly Lys Cys Pro Leu Pro Arg Gln Gln Val Thr Glu Ile Ile Phe 340 345 350 gtt tta aaa gca gtc agt act ctt att gat tca ctt aag aaa act cag 1104 Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys Thr Gln 355 360 365 cct gag aat gtt gat gga aat acc tgg gca caa gta att gcc tta tac 1152 Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala Leu Tyr 370 375 cca act tta gta gaa tgc atc acc tgt tct tct tca gaa gtc tgt tct 1200 Pro Thr Leu Val Glu Cys Ile Thr Cys Ser Ser Ser Glu Val Cys Ser 385 390 395 400 gca ctt aaa gag gca cta gtt cct ttt aag gat ttc atg cag cca cca 1248 Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe Met Gln Pro Pro 405 410 415 gca tcc aga gtt caa aat gga gaa tct tga 1278 Ala Ser Arg Val Gln Asn Gly Glu Ser \* 420 425 <210> 238 <211> 425 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(425) <223> Xaa = Any Amino Acid <400> 238 Met Asp Asp Leu Gln Lys Leu Gly Val Ile Leu His Ser Ala Ile Ser 10 Val Pro Ile Ser Ser Asp Ala Ser Pro Phe Ile Leu Pro Ser Tyr Thr 25 30 Glu Ala Val Leu Thr Ser Leu Gln Glu Ala Val Leu Thr Ala Leu Asp 35 40 45

Val	Leu 50	Gln	Lys	Ala		Cys 55	Val	Gly	Pro	Glu	Asn 60	Met	Gln	Пe	Met
Tyr 65	Pro	Ala	Ile	Phe	Asp 70	Gln	Leu	Leu	Ala	Phe 75	Val	Glu	Phe	Ser	Cys 80
Lys	Pro	Pro	Gln	Tyr 85	Gly	Gln	Xaa	Glu	Thr 90	Lys	His	Ile	Ala	Asn 95	Ala
Lys	Tyr	Asn	Gln 100	Пe	Gln	Leu	Phe	Ala 105	Pro	Ala	Glu	Trp	Val 110	Ala	Leu
Asn	Tyr	Val 115	Pro	Phe	Ala	Glu	Arg 120	Ser	Leu	Glu	Val	Val 125	Val	Asp	Leu
Tyr	Gln 130	Lys	Thr	Ala	Cys	His 135	Lys	Ala	Val	Val	Asn 140	Glu	Lys	Val	Leu
Gln 145	Asn	Ile	Ile	Lys	Thr 150	Leu	Arg	Val	Pro	Leu 155	Ser	Leu	Lys	Tyr	Ser 160
Cys	Pro	Ser	Glu	Ser 165	Thr	Trp	Lys	Leu	Ala 170	Val	Ser	Ser	Leu	Leu 175	Arg
Val	Leu	Ser	Ile 180	Gly	Leu	Pro	Val	Ala 185	Arg	Gln	His	Ala	Ser 190	Ser	Gly
Lys	Phe	Asp 195	Ser	Met	Trp	Pro	G1u 200	Leu	Ala	Asn	Thr	Phe 205	Glu	Asp	Phe
Leu	Phe 210	Thr	Lys	Ser	He	Pro 215	Pro	Asp	Asn	Leu	Ser 220	Ile	Gln	Glu	Phe
225	_				230	·				235				Ser	240
Glu	Ile	Leu	Pro	Tyr 245	Ala	Asn	Phe	Ile	Pro 250	Lys	Glu	Phe	Val	Gly 255	Gln
			260				_	265					270	Ser	
Phe	Thr	G1u 275	Ą٦a	Glu	Пе	Asp	Ile 280	Arg	Leu	Arg	G1u	G1u 285	Phe	Ser	Lys
	290					295					300		-	Val	
Thr 305	Pro	Gln	Glu		Tyr 310		Ser	Arg		A1a 315		Ser	Val	Leu	Leu 320
Lys	Arg	Ser	Gln	Asp 325	Val	Leu	His	Arg	Tyr 330	Пe	Glu	Asp	Glu	Arg 335	Leu
Ser	Gly	Lys	Cys 340	Pro	Leu	Pro	Arg	G1n 345	Gln	Val	Thr	Glu	11e 350	He	Phe
Val	Leu	Lys 355	Ala	Val	Ser	Thr	Leu 360	He	Asp	Ser	Leu	Lys 365	Lys	Thr	Gln
Pro	G1u 370	Asn	Val	Asp	Gly	Asn 375	Thr	Trp	Ala	Gln	Va1 380	Ile	Ala	Leu	Tyr
Pro 385	Thr	Leu	Val	Glu	Cys 390	Ile	Thr	Cys	Ser	Ser 395	Ser	Glu	Va1	Cys	Ser 400

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Ala	Ser	Arg	Va1 420	Gln	Asn	Gly	Glu	Ser 425								
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_		_		_									gaa Glu 30		-	96
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_		_				_		_	_	-	_		att Ile			192
		-				-		_	_	-			tgg Trp			240
	_	-	_	-				-	_			-	gtc Val			288
					-		-	-			_		gtc Val 110			336
tgg	ttg	gct	aaa	999	ctt	gga	gct	tgt	acc	tcc	agg	ССС	ata	cat	cct	384

Trp	Leu	Ala 115	Lys	Gly	Leu	G1y	Ala 120	Cys	Thr	Ser	Arg	Pro 125	Ile	His	Pro	
											cac His 140					432
	-					-					atg Met					480
											gct Ala					528
_	•						-		-		cag Gln	-	-	_	-	576
•	-	•	•								ctt Leu		_	-	-	624
_		_		_		-		_			cat His 220			-		672
		_		-	-	-		-			gca Ala		_		-	720
_			•								cgc Arg		-			768
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aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	caa	gga	912

Thr	Gly 290	Glu	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	Ala 300	Ala	Ser	Gln	Gly	
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	gac Asp		-	•	_	_	-			_			-			1008
	atc Ile													taa *		1053
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MΩT										A	^		۸7 <u> </u>		1	
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1	Phe		Glu	5				Val	10				Glu	15		
1 Ser		Ala His	G1u 20	5 Ser	Trp	Asp	Asn Leu	Va1 25	10 Gly	Leu	Leu	Val Asp	G1u 30	15 Pro	Ser	
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1 Ser Pro Glu Tyr 65 Trp	Phe Pro Val 50 His	Ala His 35 Met Pro Glu	Glu 20 Thr Glu Pro Arg	5 Ser Val Glu Ile Leu 85	Trp Asn Val Phe 70 Val	Asp Thr Leu 55 Arg	Asn Leu 40 Gln Pro Arg	Val 25 Phe Lys Met Ala	10 Gly Leu Lys Lys Leu 90	Leu Thr Ala Arg 75 Glu	Leu Asn Asp 60 Ile Asn	Val Asp 45 Leu Thr Arg	Glu 30 Leu Ile Trp Val	15 Pro Thr Leu Asn Gly 95	Ser Glu Ser Thr 80 Ile	
1 Ser Pro Glu Tyr 65 Trp	Phe Pro Val 50 His	Ala His 35 Met Pro Glu Pro	Glu 20 Thr Glu Pro Arg His 100	5 Ser Val Glu Ile Leu 85 Thr	Trp Asn Val Phe 70 Val Ala	Asp Thr Leu 55 Arg Ile Tyr	Asn Leu 40 Gln Pro Arg Asp Ala	Val 25 Phe Lys Met Ala Ala 105	10 Gly Leu Lys Lys Leu 90 Ala	Leu Thr Ala Arg 75 Glu Pro	Leu Asn Asp 60 Ile Asn Gln	Val Asp 45 Leu Thr Arg Gly	Glu 30 Leu Ile Trp Val Val	15 Pro Thr Leu Asn Gly 95 Asn	Ser Glu Ser Thr 80 Ile Asn	
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Glu	Giu	GIN	180	arg	пе	ASTI	Leu	185	Cys	ınr	GIN	Lys	190	Leu	met	
Gln	Val	Val 195	Asp	Phe	Leu	Ser	Arg 200	Asn	Lys	Gln	Leu	Tyr 205	Gln	Lys	Thr	
Glu	Ile 210		Ser	Leu	Glu	Lys 215	Pro	Leu	Leu	Leu	His 220	Thr	Gly	Met	Gly	
Arg 225		Cys	Thr	Leu	Asp 230		Ser	Val	Ser	Leu 235	Ala	Thr	Met	Пe	Asp 240	
Arg	Ile	Lys	Arg	His 245	Leu	Lys	Leu	Ser	His 250	Ile	Arg	Leu	Ala	Leu 255	Gly	
Val	Gly	Arg	Thr 260	Leu	Glu	Ser	Gln	Va1 265	Lys	Val	Val	Ala	Leu 270	Cys	Ala	
Gly	Ser	G1y 275	Ser	Ser	Val	Leu	G1n 280	Gly	Val	Glu	Ala	Asp 285	Leu	Tyr	Leu	
Thr	G1y 290	Glu	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	A1a 300	Ala	Ser	Gln	Gly	
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Ile	Ile	Leu	Ser 340	Glu	Thr	Asp	Arg	Asp 345	Pro	Leu	Gln	Val	Val 350			
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_		His		_		ctc Leu	_	-			_			_	336
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_					-	agt Ser 135		-	_				-	-	432
_	-	-				cag Gln	_	_	-						480
	_	_	_		_	ggt Gly		_	-						528
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•	-		-			agt Ser 215			_		_	_		-	672

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Gln	Val	Va1 35	20 Val	Glu	Ser	Leu	Tyr 40	25 Ile	Пе	Ser	Cys	Tyr 45	30 Gly	Thr	Leu		
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358

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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
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Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
                        135
                                            140
Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
145
                    150
                                        155
His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
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Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Val Leu Gln
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Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
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Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
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                                            220
Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Arg Gly
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                                        235
Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
                                    250
                245
Thr Leu Leu Glu Val Cys Gly Ser Trp Pro Glu Gly Phe Gly Leu Arg
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                                                    270
           260
His Met Ser Ser Met Glu His Thr Glu Glu Gly Ser Gly Ser Asp Leu
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359

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						gac Asp 55	_				-		_			192
	-	-			-	aag Lys		-		_	-		-			240
	_		-			gct Ala									_	288
	_	-		_	_	gtc Val	_	_				Lys	-	-	-	336
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Arg Tyr Glu Pro Ser Asp Lys Asp Arg Gln Ser Pro Pro Pro Ala Lys
Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
                        55
Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
                                    90
Ser Lys Ser Ser Ser Lys Val Thr Ser Val Pro Gly Lys Ala Ser Asp
                                105
Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
                            120
                                                125
Arg Glu Glu Leu Leu Lys Gln Leu Lys Ala Val Glu Asp Ala Ile Ala
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Arg Lys Arg Ala Lys Ile Pro Gly Lys Ala
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Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
 1
                 5
                                     10
                                                         15
ctc ctc gca ggg ctt gca cta ctg gga gtc ggg ccg gtc cca gcg cgg
                                                                       96
Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
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			20					25					30			
	_				_	-	-		ttt Phe		-		_			144
			-			-			tcc Ser	-	-	_	_	-		192
		-		-			_		atc Ile	-		_	_	-	-	240
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									ggg Gly							336
	-		-						ccc Pro				-	-	_	384
				-					caa G1n					_		432
									ttt Phe		-					480
									gat Asp 170							528
_			_		_				gga Gly							576
						-			cga Arg						_	624

		195					200					205				
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_		-			-	acc Thr		-		_			-		•	720
_					-	agt Ser			_	-					_	768
						gca Ala							_			816
-	-			-		ggc Gly	-	-	-			-		_	•	864
						tct Ser 295										912
						ggc Gly										960
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				-	-	ggc Gly			_	-	_	•			•	1056
				-		cag Gln	-	_			_			_		1104
				-		gaa Glu			-	_	_			-		1152

	370					375			•		380					
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		-			-	gat Asp			_	-		-			_	1248
				-		gat Asp		-								1296
	-	-	-	-		ttt Phe	-		-		-		-		•	1344
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					_	tat Tyr			_	_	-		~		•	1440
				_		caa Gln		-			-			-		1488
						ctt Leu					_	-				1536
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-						gca Ala 535						_			•	1632
						gtc Val										1680

545					550					555					560	
	aca Thr															1728
	tgt Cys	-												_	_	1776
_	aaa Lys	-	_	-							-					1824
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1 Leu Ala Thr Phe 65 Asn Ser Gln	Ala Leu Leu Leu 50 Val Ala	213> 400> Ala Ala His 35 Ala Leu Pro Leu Asp 115	Homo 246 Ala Gly 20 Asn Ala Arg Tyr Ile 100 Val	Gly 5 Leu Val Phe Glu Phe 85 Thr	Arg Ala Thr Gly Arg 70 Lys Ser Leu	Leu Leu Ala Asp 55 Asn Pro Val	Leu Glu 40 Leu Asp Lys Val Tyr 120	Gly 25 Leu Asn Leu Val Pro 105 Leu	10 Val Phe Ser Ile Lys 90 Gly Pro	Gly Gly Asp Val 75 Val Asp	Pro Ala Lys 60 Phe Ser Tyr Asn	Val Glu 45 Gln Leu Phe Asp Tyr 125	Pro 30 Ala Thr Ala Lys Gly 110 Ala	15 Ala Trp Asp Asp Asn 95 Asp Lys	Arg Gly Leu Gln 80 His Ser	

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Phe	Glu	A1a 435	Asp	Ala	Tyr	Phe	Va1 440	Lys	Val	He	Val	Leu 445	Ser	Gly	Leu
Cys	Ser 450	Asn	Asp	Cys	Pro	Arg 455	Lys	He	Thr	Pro	Phe 460	Gly	Val	Asn	Gln
Pro 465	Gly	Pro	Tyr	Ile	Met 470	Tyr	Thr	Thr	Val	Asp 475	Ala	Asn	Gly	Tyr	Leu 480
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Gln	Leu	Pro	Tyr	Asn	Val	Leu	Gly	Leu	Gly	Ara	Ser	Ala	Asn	Phe	Leu

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Asp	His	Leu 515	Tyr	Val	Gly	Ile	Pro 520	Arg	Pro	Ser	Gly	G1u 525	Lys	Ser	Ile	
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Ile 545	Pro	Tyr	Pro	His	Asn 550	Val	Pro	Arg	Ser	Trp 555	Ser	Ala	Lys	Leu	Tyr 560	
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65					70					75					80	
	gga Gly															288
	cat His	-				-			-	-						336
	gca Ala	_	Phe	-				_				-	-		-	384
	cga Arg 130	-			_	_	-			_					_	432
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373

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	-				-			-				tcc Ser	-	-		336
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WO 01/29221

48

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Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Lys Glu Leu Lys
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Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
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Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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	acc Thr														144
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	ctg Leu	-									_		_		240
_	att Ile	-	-		-	 	-	_	_	_	-				288
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	tct Ser	_	_	_								_			384
	ttt Phe 130		_		-	-	-	_	-	-		-			432
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20 25 30

378

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_							_		-		-	_	_	cag Gln	-	192
	~ ~		_			-		-			-		_	cgg Arg		240
•	_	_	_	~ ~									-	act Thr 95		288
				-				_	_		_			ctt Leu		336
	_	_		_		_			-	-		_		ctt Leu		384
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Val	Gln	Lys	Gln	Gly 85	Phe	His	His	Leu	Trp 90	Leu	Gln	Arg	Asp	Thr 95	Pro	
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	Asp	115					120					125				
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	_	_				gga Gly	-						-	_	-	528
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_					_	gtg Val	-								-	816
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295

290

285

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				-		gct Ala		-		-		-			ttc Phe	1008
	-	-		_	_	tca Ser	-	_	-		_	-	_		-	1056
_	-					ctg Leu										1104
	_			-		ccc Pro 375			-							1152
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<212> PRT

<213> Homo sapiens

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Glu	Arg	Thr 35	Ser	Gly	Gly	Pro	G1u 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Ser	Leu 50	Gly	Ser	Ser	Arg	Va1 55	Pro	Arg	Cys	Gly	Gln 60	Gly	Thr	Leu	Leu
65			-		70					75				Leu	80
His	Cys	Ser	Pro	A1 a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr
		115				•	120					125		Arg	
Tyr	His 130	Arg	Ala	Ser	Asp	Thr 135	Pro	Ser	Gly	Leu	Ser 140	Pro	Thr	Asp	Thr
145	•				150					155				Glu	160
Trp	Arg	Pro	Gln	Ala 165	Leu	Trp	Ala	Val	Pro 170	Pro	Ala	Ala	Arg	Leu 175	Ala
			180					185					190	Glu	
Pro	Val	G1n 195		Leu	Val	Ala	A1a 200	Leu	Leu	Ala	Gln	Leu 205	Cys	G1n	Pro
	210					215		•	-		220		_	Leu	
225			•		230					235				Ala	240
			·	245					250					Leu 255	
	_		260					265					270	His	
-		275	-				280					285		Val	
Leu	G1u 290	Cys	Tyr	Thr	Val	Pro 295	Pro	Glu	Asp	Asn	Leu 300	Ala	Leu	Leu	Gln
305	•		_		310			-		315				Trp	320
Pro	Val	Leu	Tyr	Ala 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	11e 335	Phe
Ser	Gln	Asp	Pro 340	Gln	Ser	Ser	Asp	G1u 345	Val	Lys	Ala	Ala	Arg 350	Arg	Ser
Met	Leu	G1n 355	Lys	Thr	Trp	Leu	Leu 360	Ala	Asp	G1u	Gly	Leu 365	Arg	Gln	His

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					ttc Phe									192
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					ctg Leu									288
					agg Arg									336

	_	atc Ile 115		•	-		_	_	_		-	_		_	384
	-	aga Arg			-										432
	•	gag Glu	-		-	-				-					480
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<213> Homo sapiens

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Thr	Ala 130		Glu	Thr	Asp	G1u 135	Asp	Glu	Asp	Asp	Val 140	Asp	Ser	۷a۱	Glu	
G1u 145	Met		Val	Thr	Ala 150		Asn	Asp	Gly	Ala 155		Thr	Asp	Gly	Val 160	
		Gln	Pro	G1u 165		Ser	Asp	Pro	Asp 170	Ala	G1n	Thr	Ile	Lys 175		
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ttc	ctc	tcc	aag	act	cgg	gtg	gtc	cag	gag	cac	ggc	ggg	cgg	gcg	gtg	336

Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105	Glu	His	Gly	Gly	Arg 110	Ala	Val	
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Gln	Val	Leu 35	Ser	Pro	Gly	Asp	Ile 40		Tyr	He	Phe	Thr 45		Thr	Pro	
Ala	Lys 50		Phe	Gly	Gly	Ile 55		His	Thr	Arg	Tyr 60		Gln	Ile	His	
Leu 65		Pro	Ala	Glu	Pro 70		Glu	Ala	Cys	Gly 75		Leu	Ser	Asn	Gly 80	
	Phe	Ile	Gln	Asp 85		Пе	Ala	Leu	Val 90		Arg	Gly	Gly	Cys 95		
Phe	Leu	Ser	Lys 100		Arg	Val	Val	G1n 105		His	Gly	G1y	Arg 110		Val	

Пe	Пe	Ser 115	•	Asn	Ala	Val	Asp 120		Asp	Ser	Phe	Tyr 125	Val	Glu	Met	
Пe	Gln 130	•	Ser	Thr	Gln	Arg 135		Ala	Asp	Ile	Pro 140	Ala	Leu	Phe	Leu	
145					150	Met				155					160	
				165		Ser			170	_			Ser	I1e 175		
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						cta Leu	-				_	_		-		144
						ggc Gly 55										192
						gtg Val			_	_		_	_	-		240
-			_			ttt Phe			-	-				_	-	288

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						gtc Val										3	884
				_		ctc Leu 135										4	132
-	_	_				ctg Leu										4	180
	_				_	tgg Trp	-				-					5	528
		_		-		aaa Lys	_				_	_	_	_		5	576
			-	_		gtg Val	_		_			_			_	6	524
	-	_	-	_	_	ctg Leu 215										6	572
-						cgg Arg										7	'20
						gaa Glu										7	'68
		_		_		acc Thr		-								8	316

			Phe		ctc Leu										-	864
		Val		_	gca Ala	_	_			-					•	912
_		-		_	ctc Leu 310	-		_			-					960
	_		-	_	cac His	_	_	-					_			1008
					ttc Phe											1056
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					ctc Leu						-		-			1152
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					agt Ser			_		_		-	_		_	1248
					acg Thr			-	-				_	_		1296
cat His	Leu				agt Ser	Val										1344

atg cac ctg ctc att aca gct gct gtc tgt gta ttc ttc acg gca atg 1392 Met His Leu Leu Ile Thr Ala Ala Val Cys Val Phe Phe Thr Ala Met 450 460 gat caa acc aga ctc aca cag tct tag 1419 Asp Gln Thr Arg Leu Thr Gln Ser \* 465 470 <210> 270 <211> 472 <212> PRT <213> Homo sapiens <400> 270 Met Val Leu Ala Ser Ala Leu Leu Cys Val Ile Val Ser Val Leu Thr 10 Asn Val Leu Val Gly Gly Asn Thr Pro Arg Lys Asn Pro Met His Pro Ser Ser Arg Trp Ser Glu Leu Asp Leu Leu Ile Leu Leu Gly Thr Ala 40 Gly His Val Leu Ser Leu Gly Ala Ser Ser Phe Val Glu Glu His 55 Gln Thr Trp Tyr Phe Leu Val Asn Thr Leu Cys Leu Ala Leu Ser Gln 70 75 Glu Thr Tyr Arg Asn Tyr Phe Leu Gly Asp Asp Gly Glu Pro Pro Cys Gly Leu Cys Val Glu Gln Gly His Asp Gly Ala Thr Ala Ala Trp Gln 105 Asp Gly Pro Gly Cys Asp Val Leu Glu Arg Asp Lys Gly His Gly Ser 120 Pro Ser Thr Ser Glu Val Leu Arg Gly Arg Glu Lys Trp Met Val Leu 135 140 Ala Ser Pro Trp Leu Ile Leu Ala Cys Cys Arg Leu Leu Arg Ser Leu 150 155 Asn Gln Thr Gly Val Gln Trp Ala His Arg Pro Asp Leu Gly His Trp 165 170 Leu Thr Ser Ser Asp His Lys Ala Glu Leu Ser Val Leu Ala Ala Leu 185 Ser Leu Leu Val Val Phe Val Leu Val Gln Arg Gly Cys Ser Pro Val 200 205 Ser Lys Ala Ala Leu Ala Leu Gly Leu Leu Gly Val Tyr Cys Tyr Arg 210 215 220

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Ile Ser Lys Gly Ile Ile Glu Ala Arg Phe Val Tyr Val Phe Val Leu
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                                    250
Gly Ile Leu Phe Thr Gly Thr Lys Asp Leu Leu Lys Ser Gln Val Ile
                                265
Ala Ala Asp Phe Lys Leu Lys Thr Val Gly Leu Trp Glu Ile Tyr Ser
                            280
Gly Leu Val Leu Leu Ala Ala Leu Leu Phe Arg Pro His Asn Leu Pro
                        295
                                             300
Val Leu Ala Phe Ser Leu Leu Ile Gln Thr Leu Met Thr Lys Phe Ile
                    310
                                        315
Trp Lys Pro Leu Arg His Asp Ala Ala Glu Ile Thr Val Met His Tyr
                325
                                    330
Trp Phe Gly Gln Ala Phe Phe Tyr Phe Gln Gly Asn Ser Asn Asn Ile
            340
                                345
Ala Thr Val Asp Ile Ser Ala Gly Phe Val Gly Leu Asp Thr Tyr Val
                            360
Glu Ile Pro Ala Val Leu Leu Thr Ala Phe Gly Thr Tyr Ala Gly Pro
                        375
                                             380
Val Leu Trp Ala Ser His Leu Val His Phe Leu Ser Ser Glu Thr Arg
                    390
                                        395
Ser Gly Ser Ala Leu Ser His Ala Cys Phe Cys Tyr Ala Leu Ile Cys
                                    410
Ser Ile Pro Val Phe Thr Tyr Ile Val Leu Val Thr Ser Leu Arg Tyr
            420
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His Leu Phe Ile Trp Ser Val Phe Ser Pro Lys Leu Leu Tyr Glu Gly
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398

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						agc Ser										288
						ctc Leu										336
			-	-		tgg Trp	_	_			_		_		_	384
						cag Gln 135										432
-						cgg Arg		-	-		-			-		480
ggt	gcc	cgt	gtg	att	gtg	aca	gac	acg	tgg	gtg	atg	aag	gta	acc	acc	528

Gly	Ala	Arg	Val	Ile 165		Thr	Asp	Thr	Trp 170	Val	Met	Lys	Val	Thr 175		
				Val							cac His				-	576
											aac Asn					624
											gct Ala 220		_	_		672
											ctc Leu					720
											atc Ile					768
											gta Val				_	816
											gcc Ala					864
											acc Thr 300					912
				Cys		Gln					ccc Pro					960
			Gly						-		gac Asp		-	_		1008
gac	acc	tgg	ctg	gcc	agc	cgc	gtg	ссс	tgc	ссс	acc	tgc	cgc	gca	cgc	1056

400

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		195					200					205				
Leu	Leu 210	Thr	Пe	Arg	Val	Ala 215	Ser	Thr	Asn	Pro	Ala 220		Gln	Ala	Phe	
Asp 225	Ile	Trp	Leu	Asn	Ser 230	Thr	Glu	Tyr	Gly	G1u 235	Leu	Cys	Glu	Lys	Leu 240	
Arg	Ala	Pro	Пe	Arg 245	Arg	Ala	Ala	His	Va1 250	Val	Ile	His	Gln	Ser 255	Leu	
Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	A1a 265	Ser	Leu	Val	Glu	Va1 270	Asn	Pro	
Ala	Tyr	Ser 275	Val	Pro	Ser	Ser	Gln 280	Glu	Leu	Glu	Ala	Cys 285	Ile	Gly	Cys	
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A1a 305	Thr	Gly	Glu	Cys	Gln 310	Gln	Cys	Tyr	Cys	Arg 315	Pro	Met	Trp	Cys	Leu 320	
Thr	Cys	Met	Gly	Lys 325	Trp	Phe	Ala	Ser	Arg 330	Gln	Asp	Pro	Leu	Arg 335	Pro	
Asp	Thr	Trp	Leu 340	Ala	Ser	Arg	Val	Pro 345	Cys	Pro	Thr	Cys	Arg 350	Ala	Arg	
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						aag Lys										96
						gct Ala										144

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										ttc Phe					336
			_		-		-		_	cat His					384
								-		tat Tyr 140					432
	-		-	_	-	_			_	aat Asn	-		_	-	480
-		 -				_		_		aat Asn				_	528
	-				-		-			atg Met	_	-			576
										tgg Trp	-		-		624
_										ctg Leu 220					672

403

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_		ı Ser Leu Ala Ala	t cgc cag aag gac a Arg G1n Lys Asp 60	
			c ctg gcc aac ctg y Leu Ala Asn Leu 5	
			c ccc cag ctc ctc y Pro Gln Leu Leu 95	
			c cct cac agc cca n Pro His Ser Pro 110	

-	_		-	_						gtg Val					384
		-	_	-			_	-		gcc Ala 140		-			432
				- •						acg Thr					480
						_	_	-	-	gac Asp			-	-	528
	_	-	_					_		ctg Leu	_	-		_	576
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## WO 01/29221

PCT/US00/29052

406

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Gln	Asp	Pro 195		Ala	Thr	Val	A1a 200	Ser	Ala	Cys	Arg	Phe 205	Ala	Leu	Arg	
Met	Cys 210	Gly	Pro	Asn	Leu	Ala 215	Cys	Glu	Glu	Leu	Ser 220	Ala	Ala	Phe	Gln	
Lys 225	His	Leu	Gln	Glu	Gly 230	Arg	Ala	Leu	His	Phe 235	Gly	Glu	Phe	Leu	Asn 240	
Thr	Thr	Cys	Lys	His 245	Leu	Met	His	His	Phe 250	Pro	Asp	Leu	Leu	Gly 255	Arg	
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	Trp	G1u 270	Asn	Val	
Arg	Ala	A1a 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu	
Pro	Arg 290	Gln	Gln	Pro	Gln	Va1 295	Asp	Leu	Asp	Gln	Leu 300	Пe	Ala	Ala	Leu	
G1n 305	Ile	Leu	Leu	Lys	Asp 310	Pro	Ala	Pro	Glu	Val 315	Arg	Thr	Arg	Ala	Ala 320	
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-		-		_	_							-	ctc Leu	_	-	144

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			-	-	-	ttt Phe			_			-		-	_	288
						ctg Leu		-	_	_	_					336
					_	aaa Lys	-	-	_					_		384
		-				caa Gln 135	_	-			-		_			432
-		-	_			tct Ser	-	_		_		-	_	-		480
-	_			_		tta Leu	_			-			-		_	528
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Asp Pro Arg Asp Val Lys Asn Met Asn Thr Trp Leu Leu Phe Leu Pro
                        55
Leu Phe Pro Val Gln Val Gln Thr Leu Ile Val Val Ile Ile Gly Met
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Leu Val Leu Leu Leu Asp Phe Leu Gly Leu Val His Leu Gly Gln Leu
Leu Ile Phe His Ile Tyr Leu Lys Ala Lys Lys Met Thr Thr Phe Glu
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Tyr Leu Ile Asn Asn Arg Lys Glu Glu Ser Ser Lys His Gln Ala Val
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Arg Lys Asp Pro Tyr Val Gln Met Asp Lys Gly Val Leu Gln Gln Gly
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Ala Gly Ala Leu Gly Ser Ser Ala Gln Gly Val Lys Ala Lys Ser Ser
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Leu Leu Ile His Lys His Leu Cys His Phe Cys Thr Ser Val Asn Gln
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Asp Gly Asp Ser Lys Ala Gln Glu Ala Asp Asp Ala Pro Ser Thr Ser
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Thr Leu Gly Leu Gln Gln Glu Thr Thr Glu Pro Met Lys Thr Asp Ser
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Tyr	Pro	Pro	Gln	Glu 165	Ala	Asn	Arg	Ser	Ile 170	Thr	Ser	Leu	Ser	Val 175	Ala	
-	act Thr	_						-				•	_		_	576
-	cct Pro				_				_							624
	gat Asp 210	_			_									-	_	672
	gat Asp	_		-	-			-			-		•			720
	ctc Leu		-	_		_				-			-	-		768
-	act Thr	_											-	_		816
	aaa Lys	_			_		_	-					_			864
-	ttg Leu 290	-	-		-					-	_		_			912
	cag Gln															960
	agt Ser		Ser					Ala				-	_		-	1008
gct	gca	cat	gaa	gct	gag	gaa	gaa	tct	gat	aat	att	gca	gaa	gac	ttc	1056

	Αla	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1ս 350	Asp	Phe		
_			_	_	gaa Glu		-				-			-	-	110	4
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Glv	Ser	Pro	Glv	Gly	Leu	Thr	Sar	t ou	C1~				0.3	۸			
u i j			-	- · · <b>J</b>	LCu	1111	261		GIII	Gln	GIn	Lys		Arg	Leu		
_		Ser	20	•	Asn		His	25				Glu	30	_			
Ile	Glu Val	Ser 35	20 Leu	Arg		Ser Pro	His 40	25 Ser	Ser	Ile	Ala Asn	G1u 45	30 Ile	Gln	Lys		
Ile Asp Ile	Glu Val 50	Ser 35 Glu	20 Leu Tyr	Arg Arg	Asn Leu Pro	Ser Pro 55	His 40 Phe	25 Ser Thr	Ser Ile	Ile Asn Gln	Ala Asn 60	Glu 45 Leu	30 Ile Thr	Gln Ile	Lys Asn Ile		
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Ile Asp Ile 65 Ser Tyr Gly Val	Glu Val 50 Asn Val Val Lys Leu 130	Ser 35 Glu Ile Tyr Thr Ile 115 Ala	20 Leu Tyr Leu Pro Ser 100 Ile Pro	Arg Arg Leu Pro 85 Pro Gln Thr	Asn Leu Pro 70 Ile Leu Ser	Ser Pro 55 Pro Arg Val Leu Thr 135	His 40 Phe Gln His Asn Leu 120 Ala	25 Ser Thr Phe His Asn 105 Asp	Ser Ile Pro Leu 90 Phe Glu Pro	Ile Asn Gln 75 Met Thr Phe	Ala Asn 60 Glu Asp Met Trp Leu 140	Glu 45 Leu Lys Lys His Lys 125 Tyr	30 Ile Thr Pro Gln Ser 110 Asn	Gln Ile Val Gly 95 Asp Pro Asn	Lys Asn Ile 80 Val Leu Pro		

Asp	Thr	Val	Ser 180	Ser	Ser	Thr	Thr	Ser 185	His	Thr	Thr	Ala	Lys 190	Pro	Ala	
Ala	Pro	Ser 195	Phe	Gly	Val	Leu	Ser 200	Asn	Leu	Pro	Leu	Pro 205	Ile	Pro	Thr	
Val	Asp 210	Ala	Ser	Пe	Pro	Thr 215	Ser	Gln	Asn	Gly	Phe 220	Gly	Tyr	Lys	Met	
Pro	Asp	Val	Pro	Asp	Ala		Pro	Glu	Leu	Ser		Leu	Ser	Val	Ser	
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Gln	Leu	Thr	Asp	Met 245	Asn	Glu	Gln	Glu	G1u 250	Val	Leu	Leu	Glu	G1n 255	Phe	
Leu	Thr	Leu	Pro 260	Gln	Leu	Lys	Gln	Ile 265	Ile	Thr	Asp	Lys	Asp 270	Asp	Leu	
Val	Lys	Ser 275	Ile	Glu	Glu	Leu	A1a 280	Arg	Lys	Asn	Leu	Leu 285	Leu	Glu	Pro	
Ser	Leu 290	Glu	Ala	Lys	Arg	G1n 295	Thr	Val	Leu	Asp	Lys 300	Tyr	Glu	Leu	Leu	
Thr	Gln	Met	Lys	Ser	Thr	Phe	Glu	Lys	Lys	Met	Gln	Arg	Gln	His	Glu	
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Ala	Ala	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe	
Leu	Glu	G1y 355	Lys	Met	Glu	Ile	Asp 360	Asp	Phe	Leu	Ser	Ser 365	Phe	Met	Glu	
Lys	Arg 370	Thr	Пe	Cys	His	Cys 375	Arg	Arg	Ala	Lys	G1u 380	Glu	Lys	Leu	Gln	
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Val	Arg	Asn	Ser 20	Lys	Lys	Arg	Pro	A1a 25	Ser	Pro	Ser	His	Asn 30	Gly	Ser	
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-			_			agc Ser 55				_	_				-	192
					_	aca Thr				-		-	-			240
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-	-	-	_			aga Arg										336
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Ser Gly Gly Gly Tyr Gly Ala Ser Lys Lys Lys Ala Ser Ala Ser
Ser Phe Ala Gln Gly Ile Ser Met Glu Ala Met Ser Glu Asn Lys Met
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Val Pro Ser Glu Phe Ser Thr Gly Pro Val Glu Lys Ala Ala Lys Pro
Leu Pro Phe Lys Asp Pro Asn Phe Val His Ser Gly His Gly Gly Ala
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Val Ala Gly Lys Lys Asn Arg Thr Trp Lys Asn Leu Lys Gln Ile Leu
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Ala Ser Glu Arg Ala Leu Pro Trp Gln Leu Asn Asp Pro Asn Tyr Phe
                            120
Ser Ile Asp Ala Pro Pro Ser Phe Lys Pro Ala Lys Lys Tyr Ser Asp
                        135
                                            140
Val Ser Gly Leu Leu Ala Asn Tyr Thr Asp Pro Gln Ser Lys Leu Arg
                   150
                                        155
Phe Ser Thr Ile Glu Glu Phe Ser Tyr Ile Arg Arg Leu Pro Ser Asp
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-		-	-	-	_	aat Asn						-		-		240
						cat His		-	-		-			-		288
						cag Gln										336
						gag Glu		_			_			_	_	384
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						aga Arg								-		528

		•			aaa Lys	-			-	_	-			-		576
_			-		gtt Val	-							-		_	624
					aaa Lys											672
					gca Ala 230											720
					ctt Leu											768
		_		-	gat Asp	_			-		-					816
	•	-			ctt Leu		-	-		-		-	_			864
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Lys	Gly	Lys 35	Gly	Arg	Asn	Thr	G1y 40	Lys	Ser	Gln	Thr	Leu 45	Gly	Ser	Lys
Ser	Thr 50	Thr	Asn	Glu	Lys	Lys 55	Arg	Glu	Lys	Arg	Arg 60	Lys	Lys	Lys	Glu
G1n 65	Gln	Gln	Ser	Glu	A1a 70	Asn	Glu	Leu	Arg	Asn 75	Leu	Ala	Phe	Lys	Lys 80
He	Pro	Gln	Lys	Ser 85	Ser	His	Ala	Val	Cys 90	Asn	Ala	Gln	His	Asp 95	Leu
Pro	Leu	Ser	Asn 100	Pro	Val	Gln	Lys	Asp 105	Ser	Arg	Glu	G1u	Asn 110	Trp	Gln
Glu	Trp	Arg 115	Gln	Arg	Asp	Glu	Gln 120	Leu	Thr	Ser	Glu	Met 125	Phe	Glu	Ala
	130		Ť		Leu	135			•		140	Ť			
Lys 145	Lys	Glu	Tyr	Glu	Asp 150	Ala	Glu	Asn	Thr	Ser 155	Thr	Gln	Ser	Lys	Val 160
Met	Asn	Lys	Lys	Asp 165	Lys	Arg	Lys	Asn	His 170	Gln	Gly	Lys	Asp	Arg 175	Pro
Leu	Thr	Val	Ser 180	Leu	Lys	Asp	Phe	His 185	Ser	Glu	Asp	His	Ile 190	Ser	Lys
Lys	Thr	G1u 195	Glu	Val	Val	Leu	Lys 200	Asp	Gly	Arg	Пe	G1u 205	Arg	Leu	Lys
Leu	Glu 210	Leu	Glu	Arg	Lys	Asp 215	Ala	Glu	Ile	Gln	Lys 220	Leu	Lys	Asn	Val
11e 225	Thr	Gln	Trp	Glu	A1a 230	Lys	Tyr	Lys	Glu	Va1 235	Lys	Ala	Arg	Asn	A1a 240
G1n	Leu	Leu	Lys	Met 245	Leu	Gln	Glu	Gly	G1u 250	Met	Lys	Asp	Lys	A1 a 255	Glu
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He	Gln	Val 275	Thr	Ser	Leu	His	A1 a 280	Ala	Leu	Glu	G1n	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	G1ņ	Ala	G1u 295	Leu	Ala	Lys	Tyr	G1n 300	Gly	Gly	Arg	Lys
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	-		-					-	act Thr			_	_		-	192
			_						gaa Glu		_			_		240
	-				_			-	acc Thr 90					-	-	288
									caa Gln							336
			_						acc Thr			_	_			384
				_	-				gag Glu		-	_	-			432
ctt	tgg	aag	cat	999	aat	ctg	cga	aat	gtg	ctg	atc	ttg	atg	gat	caa	480

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-		-			tct Ser				-	-				-	-	624
	-	_	_	_	gaa Glu	_	_							_		672
					gac Asp 230						_	-			_	720
					ttt Phe											768
					gag Glu								-			816
			Phe		gaa Glu	Glu	Ile	Lys	Lys	_	Leu					864
					ccc Pro											912
				-	att Ile 310			-			_					960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008

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	atc Ile											-			• •	1104
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	acc Thr															1200
•	ctc Leu		•		-		-	_	-		_	•	_	•	_	1248
-	gag Glu	-	-	-					_		_				_	1296
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G1n 65	Ala	Met	Arg	Glu	Gly 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asn 80	
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∏e	Met	Glu 115	Gln	Leu	Leu	Ser	Ser 120	Leu	Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr	
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			180					185					Lys 190			
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	210					215		-			220		Ile			
225	•		•		230					235			Ile		240	
				245					250				Arg	255		
			260			•		265					Arg 270		·	
		275					280			•		285	Ser			•
	290		•			295				_	300		Cys		•	
305				-	310				•	315				·	320	
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Leu 385	Thr	Ser	Gln	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395	Glu	Gln	Leu	Thr	Thr 400	

Arg	Leu	Gln	Ala	Leu 405	Arg	Gln	Asp	Pro	Cys 410	Ile	Ser	Val	Gln	Arg 415	Ala	
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-		-			-							agc Ser				144
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			100	-	=	-	•	105	-		-		110			

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_						ctt Leu 135	_			-	_				_	4	432
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		-		-	-	cag Gln				-	-	-	-	-	-	į	528
	-	_				ctg Leu							-			į	576
	-			_		agg Arg		-					-		-	(	624
					_	atg Met 215	-		-				*			(	672
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426

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Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	G1n	Cys 140	Gly	Leu	Gln	Ala		
-		-		-					gtg Val		-						480
		-	-						ccc Pro 170						_	!	528
									ggc Gly							!	576
		-		-					caa G1n					-		•	624
	_					-	_		acg Thr	_		•	_		_	(	672
		_	-	-	_				gca Ala						_	•	720
	_		cgt Arg			gag Glu	tag *										7 <b>4</b> 4
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Phe	Ser	Gly	Val 20	Glu	Ser	Ala	Leu	Ser 25	Ser	Leu	Lys	Asn	Phe 30	Gln	Ala		
Cys	Пe	Asn 35	Ser	Gly	Met	Asp	Thr 40	Ala	Ser	Ser	Val	A1a 45	Leu	Asp	Leu		

428

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Val Glu Ser Gln Thr Glu Val Ser Ser Glu Tyr Ser Met Asp Lys Ala
    50
                         55
                                             60
Met Val Glu Phe Ala Thr Leu Asp Arg Gln Leu Asn His Tyr Val Lys
                    70 '
Ala Val Gln Ser Thr Ile Asn His Val Lys Glu Glu Arg Pro Glu Lys
Ile Pro Asp Leu Lys Leu Leu Val Glu Lys Lys Phe Leu Ala Leu Gln
                                 105
Ser Lys Asn Ser Asp Ala Asp Phe Gln Asn Asn Glu Lys Phe Val Gln
                            120
                                                 125
Phe Lys Gln Gln Leu Lys Glu Leu Lys Lys Gln Cys Gly Leu Gln Ala
Asp Arg Glu Ala Asp Gly Thr Glu Gly Val Asp Glu Asp Ile Ile Val
                    150
                                        155
Thr Gln Ser Gln Thr Asn Phe Thr Cys Pro Ile Thr Lys Glu Glu Met
                165
                                    170
Lys Lys Pro Val Lys Asn Lys Val Cys Gly His Thr Tyr Glu Glu Asp
            180
                                185
Ala Ile Val Arg Met Ile Glu Ser Arg Gln Lys Arg Lys Lys Ala
                            200
Tyr Cys Pro Gln Ile Gly Cys Ser His Thr Asp Ile Arg Lys Ser Asp
                        215
                                            220
Leu Ile Gln Asp Glu Ala Leu Arg Arg Ala Ile Glu Asn His Asn Lys
225
                    230
                                        235
                                                             240
Lys Arg His Arg His Ser Glu
                245
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                                     10
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48

_	-			-	_	-		gag Glu 25		_		-				96
_		-	-					agc Ser			-		-		-	144
	_	-	_					ctg Leu						-		192
-	-					_		ctc Leu	-		-	-		_	-	240
		-		-	-	-	_	acc Thr				-				288
•	_				_	-	-	999 Gly 105	-				-			336
-	_		-	_	-			gcg Ala		-			-			384
		_	_	-				ctg Leu			_		_			432
								gag Glu								480
								tgc Cys								528
								ctg Leu 185								576

-	-		_	-	acc Thr			-	-	-			-	-	_	624
-	_				ctg Leu	_	-					_	-		-	672
		•	_		ggc Gly 230	-	-	-								720
		_	-		ctg Leu	_					-	_	_		_	768
	_			_	ctg Leu				_	_	_				_	816
_	_	-	-		ctg Leu					-		_		_		864
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<213> Homo sapiens

<220>

<221> VARIANT

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Ala	Cys	Thr	His 20	Ser	Ser	Ala	Tyr	G1u 25	Asn	Gln	Arg	Val	Thr 30	Thr	Thr
Ala	Phe	Leu 35	Ala	Glu	Leu	Leu	Asn 40	Ser	Asn	Val	Ala	Asn 45	Asp	Leu	Met
Leu	Leu 50	Asp	Ser	Leu	Leu	Glu 55	Ser	Leu	Ala	Ala	Arg 60	Gln	Lys	Asp	Thr
Cys 65	Ala	Xaa	Val	Arg	Arg 70	Leu	Val	Leu	Arg	Gly 75	Leu	Ala	Asn	Leu	A1a 80
Ser	Gly	Cys	Pro	Asp 85	Lys	Val	Arg	Thr	His 90	Gly	Pro	G1.n	Leu	Leu 95	Thr
Ala	Met	Ile	Gly 100	Gly	Leu	Asp	Asp	Gly 105	Asp	Asn	Pro	His	Ser 110	Pro	Val
Ala	Leu	Glu 115	Ala	Met	Leu	Gly	Leu 120	Ala	Arg	Leu	Val	His 125	Leu	Val	Glu
Ser	Trp 130	Asp	Leu	Arg	Ser	Gly 135	Leu	Leu	His	Val	Ala 140	Пe	Arg	Ile	Arg
145			·		150					155		Ala			160
Leu	Phe	Gly	His	Leu 165	Asn	Lys	Val	Cys	His 170	Gly	Asp	Cys	Glu	Asp 175	Val
		·	180				-	185				Leu	190		
G1n	Asp	Pro 195	Gln	Ala	Thr	Val	Ala 200	Ser	Ala	Cys	Arg	Phe 205	Ala	Leu	Arg
Met	Cys 210	Gly	Pro	Asn	Leu	Ala 215	Cys	Glu	Glu	Leu	Ser 220	Ala	Ala	Phe	Gln
Lys 225	His	Leu	Gln	Glu	G1y 230	Arg	Ala	Leu	His	Phe 235	G1y	Glu	Phe	Leu	Asn 240
Thr	Thr	Cys	Lys	His 245	Leu	Met	His	His	Phe 250	Pro	Asp	Leu	Leu	G1y 255	Arg
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	Trp	G1u 270	Asn	Val
Arg	Ala	A1a 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu
Pro	Arg 290	Gln	Gln	Pro	Gln	Va1 295	Asp	Leu	Asp	Gln	Leu 300	Пe	Ala	Gly	Glu
His 305	Pro	Ser	Thr	Gly	Pro 310	Leu	Arg	Trp	Ala	Leu 315	Leu	Thr	Leu		

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								cgc Arg								144
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-		-	-	-	-	-		tac Tyr	-				-	-	-	240
		_			_		-	tgg Trp		-	-					288
		-	-		_	_	_	aga Arg 105			_					336
	_				_			gag Glu				_				384
								agt Ser								432

	Glu							gtg Val 155						480
			_			-	_	ccc Pro						528
								cta Leu						576
								agt Ser		_	_	_	_	624
								aac Asn	-		_	_		672
		-	 _	-	_	 		ttg Leu 235	•			•		720
								caa G1n						768
								ttt Phe	-		-			816
ctg Leu								aaa Lys						864
				Thr				gac Asp	_		_	-		912
			Gln					cca Pro 315						960

434

-	_				atc Ile				-	-	_		_	1008
_		-	-	 -	gtg Val	_	-	-	_			-	~ ~	1056
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tga *						•								1107
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<211> 368

<212> PRT

<213> Homo sapiens

<400> 294

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 20
 25
 30

 Asp Ile Leu Asp Met Lys Glu Ser Arg Gln Val Pro Gly Val Phe Leu
 35
 40
 45

 Tyr Asn Gly His Pro Ile Lys Gln Val Asp Val Leu Gly Thr Val Ile
 50
 60

 Gly Val Arg Glu Arg Asp Ala Phe Tyr Ser Tyr Gly Val Asp Asp Ser
 60

 Thr Gly Val Ile Asn Cys Ile Cys Trp Lys Lys Leu Asn Thr Glu Ser
 80

 Thr Gly Val Ile Asn Cys Ile Cys Trp Lys Lys Leu Asn Thr Glu Ser
 90

 Val Ser Ala Ala Pro Ser Ala Ala Arg Glu Leu Ser Leu Thr Ser Gln
 100

 Leu Lys Lys Leu Gln Glu Thr Ile Glu Gln Lys Thr Lys Ile Glu Ile
 125

 Gly Asp Thr Ile Arg Val Arg Gly Ser Ile Arg Thr Tyr Arg Glu Glu
 130

 Arg Glu Ile His Ala Thr Ala Tyr Tyr Lys Val Asp Asp Pro Val Trp

 140

 Arg Glu Ile His Ala Arg Met Leu Glu Leu Pro Thr Ile Tyr Arg Lys

				165					170					175		
Val	Tyr	Asp	Gln 180	Pro	Phe	His	Ser	Ser 185	Ala	Leu	Glu	Lys	Glu 190	Glu	Ala	
Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu	
Ser	Glu 210		Ala	Lys	Glu	Phe 215		Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe	
Tyr 225		Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235		Ser	Leu	Ala	Asn 240	
Gln	Pro	Val	Ile	His 245	Ser	Ala	Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255		
Asp	Thr	Thr	Ser 260	Lys	Ala	Ile	His	Ser 265	Ile	Phe	Lys	Asn	A1a 270	Ile	Gln	
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Val 280	Phe	Gln	Lys	Asp	Asp 285	Gly	Phe	Asp	
Asn	Leu 290	Tyr	Tyr	Val	Thr	Arg 295	Glu	Asp	Lys	Asp	Leu 300	His	Arg	Lys	Ile	
His 305	Arg	Ile	Пe	G1n	G1n 310	Asp	Cys	Gln	Lys	Pro 315	Asn	His	Met	Glu	Lys 320	
				325					330			Leu		335	_	
			340					345				Glu	350			
Asp	Gln	Ser 355	Asp	Ile	Val	Ser	Thr 360	Met	Glu	His	Tyr	Tyr 365	Thr	Ala	Phe	
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Met 1	Ile <sup>°</sup>	Lys	Ser	Ala 5	Pro	Val	Gly	Pro	Val 10	Ala	Gly	G1y	Ile	Met 15	Gly	
												cgc Arg				96

	_	 _		_		_			ctt Leu	_	_	_	-		144
									aga Arg						192
-		_	_	_				_	aac Asn 75				-		240
									gaa Glu						288
									ggt Gly		_	-	_	,	336
	_	 _	-	-				-	aac Asn		_	_		,	384
									gac Asp					,	432
							_		aag Lys 155					,	480
									cac His					,	528
_	-	act Thr 180	-	-	-	-	_	taa *							558

<210> 296

<211> 185

<212> PRT

437

<213> Homo sapiens

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1 5 10 15

gtc agc aac gat ccc gat gtc atc aag ttg caa gag att cca acc ttc 96 Val Ser Asn Asp Pro Asp Val Ile Lys Leu Gln Glu Ile Pro Thr Phe

			20					25					30				
						cta Leu											144
-		-			-	gac Asp 55		_	-		_	•		_			192
-			-		_	cat His	_	_	_		-	-	-		•		240
-		-	-	-		cga Arg				_	-	-		-	•		288
	-		-		_	cag Gln		-	-		_		-	_			336
						gtg Val											384
						cag Gln 135					_	-				•	432
_						gag Glu						-	_	-		•	480
-			ctc Leu		ctg Leu	tag *										;	501

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<211> 166

<212> PRT

<213> Homo sapiens

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			- 20			25			30		
				att Ile		Met					144
		Ser		ctt Leu							192
	Arg			aaa Lys 70							240
				act Thr							288
				att Ile							336
				aat Asn							384
				cgt Arg							432
				cgg Arg 150							480
				agc Ser							528
		Arg		tca Ser							576
				gtt Val							624

		195					200					205				
			gag Glu													672
			aca Thr													720
	_	-	cag G1n							-					-	768
			agc Ser 260											_		816
	tat Tyr		tga *													 828
	<2 <2	210> 211> 212> 213>	275	sap	oiens	;										
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_	Ala	Ala	Asp 20	_	Leu	Asn	Arg	Arg 25		Пe	Val	Gln	Asp 30		Gly	
Cys	Leu	Pro 35	Gly	Leu	Ile	Leu	Phe 40		Asp	His	Pro	Asn 45		Pro	Val	
Val <sup>.</sup>	His 50		Ala	Leu		A1a 55		Arg	Tyr	Leu	A1 a 60		Cys	Arg	Ala ·	
Asn 65		Glu	Lys	Met			Glu	Leu	Gly ·	Met 75		Leu	Ser	Leu	G1n 80	

Asn	Val	Ile	Gln	Lys 85	Thr	Thr	Thr	Pro	G1y 90	Glu	Thr	Lys	Leu	Leu 95	Ala	
Ser	Glu	Пe	Tyr 100	Asp	Ile	Leu	Gln	Ser 105	Ser	Asn	Met	Ala	Asp 110	Gly	Asp	
Ser	Phe	Asn 115	Glu	Met	Asn	Ser	Arg 120	Arg	Arg	Lys	Ala	Xaa 125	Phe	Phe	Leu	
Gly	Thr 130	Thr	Asn	Lys	Arg	Ala 135	Lys	Thr	Val	Val	Leu 140	His	Ile	Asp	Gly	
Leu 145	•	Asp	Thr	Ser	Arg 150	Arg	Asn	Leu	Cys	G1u 155	Glu	Ala	Leu	Leu	Lys 160	
He	Lys	Gly	Val	Ile 165	Ser	Phe	Thr	Phe	Gln 170	Met	Ala	Val	Gln	Arg 175	Cys	
Val	Val	Arg	Ile 180	Arg	Ser	Asp	Leu	Lys 185	Ala	Glu	Ala	Leu	Ala 190	Ser	Ala	
Ile	Ala	Ser 195	Thr	Lys	Val	Met	Lys 200	Ala	Gln	Gln	Val	Val 205	Lys	Ser	Glu	
	210				Leu	215					220					
225					Leu 230					235		-			240	
	•			245	Lys				250		•			255		
			Ser 260	Trp	Leu	Ser	Thr	A1a 265	Ala	Asn	Phe	Leu	Ser 270	Arg	Ser	
Phe	Tyr	Trp 275														
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				_	ture											•
					101) C or											
		00>														
			_	_	ctt Leu	_		-				-		_		48
•				9					10					10		

														cct Pro			6
				_				_						agc Ser	_	14	4
							-			-	-		-	aag Lys	•	19	2
-		_	_	_	-							_		aag Lys	aaa Lys 80	24	0
		_					-	-			_			gat Asp 95		28	8
	_				_	_	_			-	_	-		tgg Trp		33	6
		-		_	-		_	_			-	_		gaa Glu	-	38	4
													-	gag Glu		43	2
			_											aaa Lys		48	0
													-	aga Arg 175		52	8
		_				-			-	-	_			agt Ser		570	6

-			gaa Glu	-	-								-			624
			aga Arg	_	-	•	-	-						-	•	672
	_	_	gaa Glu	-			-					_		-		720
-,		-	cac His		_	_			_		-		_		-	768
-		-	tta Leu 260			-			-	-	-		-	_	-	816
		-	atc Ile											_	-	864
_		-	caa Gln		-		_		_	-		-	-		-	912
_	_	-	ata Ile		_		_	_	_			_		-		960
-			att Ile	_						_	-		-		•	1008
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			999 Gly					_		-				tga *		1101

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				245					250					255		
Arg	Leu	Lys	Leu 260	Glu	Leu	G1u	Arg	Lys 265	Asp	Ala	Glu	Пe	G1n 270	Lys	Leu	
Lys	Asn	Va1 275	Ile	Thr	Gln	Trp	G1u 280	Ala	Lys	Tyr	Lys	G1u 285	Val	Lys	Ala	
Arg	Asn 290	Ala	Gln	Leu	Leu	Lys 295	Met	Leu	Gln	Glu	Gly 300	Glu	Met	Lys	Asp	
Lys 305	Ala	Glu	Ile	Leu	Leu 310	G1n	Val	Asp	Glu	Ser 315	Gln	Ser	Ile	Lys	Asn 320	
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Arg	Ser	Lys	Va1 340	Lys	Val	Leu	Gln	Ala 345	Glu	Leu	Ala	Lys	Tyr 350	Gln	Gly	
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_			_	_	act Thr	_	_	_		-	, -	-	-		-	624
gat Asp			_		ata Ile		_	-	_					-	-	672
gtt Val 225			-	-	ctg Leu 230		_	_			_			-	-	720
	-	-	_		ttc Phe	-	_			_			_			768

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235

Phe Glu Asp Lys Trp Phe Arg Lys Ile Lys Asp His Phe Cys Pro Phe

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		gca Ala				-	-	_		_	_			-	•	384

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	115			120			125				
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ttc Phe											480
cac His											528
agt. Ser											576
tgt Cys											624
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WO 01/29221

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			-			act Thr					-	-		_		336
						cga Arg										384
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-		_			_	ttg Leu	-		-		-			-		768
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Lys	Thr	A1a 35		Leu	Asp	Tyr	Ile 40		Arg	Cys	Arg	Pro 45		Asp	Ser	
Glu	Lys		Asn	Met	Ile	Ala		Cys	Phe	Ser	Met		Arg	Glu	Пе	

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Ala	Lys	Asp 115	Ser	Cys	Val	Arg	Gln 120	Ala	Gln	His	Cys	Gln 125	Arg	Leu	Thr	
Lys	Leu 130	Ile	Thr	Leu	Gln	Ile 135	His	Phe	Leu	Asn	Thr 140	Gly	Gln	Asn	Thr	
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Leu	Pro	Arg	Phe	Tyr 165	Gln	Ala	Ser	He	Val 170	Ala	Glu	Ala	Tyr	Asp 175	Phe	
Val	Pro	Asp	Trp 180	Ala	Glu	Ile	Leu	Tyr 185	Gln	Gln	Val	Ile	Leu 190	Lys	Gly	
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Ser	Ile 210	Phe	Glu	Glu	Пe	Ser 215	Lys	Lys	Tyr	Lys	G1n 220	His	Gln	Pro	Thr	
225					230	Leu				235			-		240	
				245		Leu			250					255		
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						•	-	-	-	cat His	-	-	-	_	-	•	144
				_		_	_			gca Ala	_	-				-	192
G			_	_	-			-		tta Leu							240
										atg Met 90							288
_		-		-		_		-		aag Lys	-			-	-	-	336
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G	1n	Leu	Tyr 35		Ser	Leu	Met	Ala 40		His	Ala	Ser	Arg 45		Arg	Val	
I	1e	Lys 50		Cys	Пe	Ala	G1n 55		Ser	Ala	Val	Va1 60		Asn	Leu	Arg	
G	٦u		Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	Gln	Leu	

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Glu	Glu	Val	Val 100	Asn	Asp	Arg	Ser	Trp 105	Lys	Val	Phe	Asn	Glu 110	Arg	Cys	
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														atc Ile		192
								-	-	-	_	-	-	gga Gly		240
							-	_						agc Ser 95		288
														gtt Val		336

			100		•			105					110		•	
	aat Asn		Asp													384
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	tcg Ser														_	480
	cta Leu															528
	cac His	_		_		tga *										549
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His	His 130		Pro	Glu	Pro	Val 135	Trp		ı Ala	Ala	Arg	Pro		Arg	Ala	
Pro 145		Ser	Trp	Gly	Ala 150	Glu		Ala	Pro	His 155	Gly		Gln	Ala	Leu 160	
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Leu Phe Asn Ser Val Ala Phe Gln Asn Ala Asp Ala Thr Arg Arg Thr
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                 5
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ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
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Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
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                                 25
gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
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						ccg Pro							-		288
	_	-		-	-	atc Ile	-	-					_	_	336
						aga Arg						-			384
						gcc Ala 135									432
						cag Gln								gac Asp 160	480
						ctg Leu									528
						tgc Cys									576
						cac His							-	-	624
Met						gga Gly 215									672

			-	gcc Ala		-	-	-			-	-	-		_	720
			-	tac Tyr 245							_	-			_	768
	_		_	gg <u>c</u> Gly							_				_	816
	-			agc Ser		_		_	_	_		-				864
	_	•	_	gat Asp	_	_				•				_	_	912
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Ala	Thr	I1e 35	Ala	Asp	Leu	Ile	Leu 40	Ser	Ala	Leu	Glu	Arg 45	Ala	Thr	۷a٦
Phe	Leu 50	Glu	Gln	Arg	Leu	Pro 55	Glu	Ile	Asn	Leu	Asp 60	Gly	Met	Val	Gly
Va1 65	Arg	۷a۱	Leu	G1u	G1u 70	Gln	Leu	Lys	Ser	Va1 75	Arg	Glu	Lys	Trp	A1 a 80
Gln	Glu	Pro	Leu	Leu 85	Gln	Pro	Leu	Ser	Leu 90	Arg	Val	Gly	Met	Leu 95	Gly
	•		100		Ala			105					110		
Ser	Asp	Pro 115	Lys	Tyr	Leu	Arg	Glu 120	Phe	Gln	Leu	Thr	Leu 125	Gln	Pro	Gly
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145				•	Pro 150		·			155			_		160
	•			165	Leu				170					175	
Cys	Gly	Leu	Ser 180	Asp	Leu	Cys	Arg	Ser 185	Leu	Met	Thr	Lys	Pro 190	Gly	Cys
	•	195	•		Ser		200					205	,		
	210				Gln	215					220				
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Glu	Ala	Ile 275	Leu	Ser	Trp	Gln	Lys 280	Gln	Gln	Glu	Gly	Cys 285	Phe	Gly	Glu
Pro	Asp 290	Ala	Glu	Asp	Glu	G1u 295	Ser	Ser	Lys	Ala	11e 300	Gln	Tyr	Gln	G1n
His 305	Phe	Ser	Arg	Arg	Val 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	Gly 320
Cys	Ser	Ser	His	Asn 325	Thr	Ala	Thr	Ala	Val 330	Ala	Ala	Leu	Gly	Gly 335	Phe
Leu	Tyr	Пe	Leu 340	Ala	Glu	Tyr	Pro	Pro 345	Ala	Asn	Arg	Glu	Pro 350	His	Pro

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														ctg Leu 95		288
-											_		-	gtg Val		336

-					ctc Leu								_	-		384
	_	_			aac Asn		-	-			-	-		_		432
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-					gag Glu	_							-			528
	_	_	_	-	atg Met											576
	-		_		cct Pro		_	_	_	-		_				624
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					ggc Gly											768
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-		_			ctg Leu			_					_			864

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	-	-	-	_		ctg Leu		-					-	-	_	1008
	_	-		_		gcc Ala					_	_			-	1056
	-		-	-	_	gaa Glu		_	_			_	•	_		1104
-						agc Ser 375	_	_		-	_	-				1152
			-			ctg Leu				-						1200
	-			_		ctạ Leu				-				-	-	1248
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Leu Met His Arg Leu Ala Pro His Cys Ser Phe Ala Arg Trp Leu Leu 20 25 30

Cys Asn Gly Ser Leu Phe Arg Tyr Lys His Pro Ser Glu Glu Glu Leu 35 40 . 45

Arg Ala Leu Ala Gly Lys Pro Arg Pro Arg Gly Arg Lys Glu Arg Trp 50 55 60

Ala Asn Gly Leu Ser Glu Glu Lys Pro Leu Ser Val Pro Arg Asp Ala 65 70 75 80

Pro Phe Gln Leu Glu Thr Cys Pro Leu Thr Thr Val Asp Ala Leu Val 85 90 95

Leu Arg Phe Phe Leu Glu Tyr Gln Trp Phe Val Asp Phe Ala Val Tyr
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Ser Gly Gly Val Tyr Leu Phe Thr Glu Ala Tyr Tyr Met Leu Gly
115 120 125

Pro Ala Lys Glu Thr Asn Ile Ala Val Phe Trp Cys Leu Leu Thr Val 130 135 140

Thr Phe Ser Ile Lys Met Phe Leu Thr Val Thr Arg Leu Tyr Phe Ser 145 150 155 160

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Phe Leu Leu Ala Met Leu Val Gln Val Arg Glu Glu Thr Leu 180 185 190

Glu Leu Gly Leu Glu Pro Gly Leu Ala Ser Met Thr Gln Asn Leu Glu
195 200 205

Pro Leu Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys

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Leu 225	Ala	Пe	Arg	Val	G1y 230	Leu	Ala	Val	Val	Gly 235	Ser	Val	Leu	Gly	A1a 240
Phe	Leu	Thr	Phe	Pro 245	Gly	Leu	Arg	Leu	Ala 250	Gln	Thr	His	Arg	Asp 255	Ala
Leu	Thr	Met	Ser 260	Glu	Asp	Arg	Pro	Met 265		Gln	Phe	Leu	Leu 270	His	Thr
Ser	Phe	Leu 275	Ser	Pro	Leu	Phe	I1e 280	Leu	Trp	Leu	Trp	Thr 285	Lys	Pro	Ile
Ala	Arg 290	Asp	Phe	Leu	His	G1n 295	Pro	Pro	Phe	Gly	G1u 300	Thr	Arg	Phe	Ser
Leu 305	Leu	Ser	Asp	Ser	Ala 310	Phe	Asp	Ser	G1y	Arg 315	Leu	Trp	Leu	Leu	Va1 320
Val	Leu	Cys	Leu	Leu 325	Arg	Leu	Ala	Val	Thr 330	Arg	Pro	His	Leu	G1n 335	Ala
			340					345					Arg 350		
Gly	Arg	I1e 355	Glu	Ala	Arg	Glu	Ile 360	Gln	Gln	Arg	Val	Val 365	Arg	Val	Tyr
Cys	Tyr 370	Val	Thr	Val	Val	Ser 375	Leu	Gln	Tyr	Leu	Thr 380	Pro	Leu	Ile	Leu
Thr 385	Leu	Asn	Cys	Thr	Leu 390	Leu	Leu	Lys	Thr	Leu 395	Gly	Gly	Tyr	Ser	Trp 400
Gly	Leu	Gly	Pro	Ala 405	Pro	Leu	Leu	Ser	Pro 410	Asp	Pro	Ser	Ser	Ala 415	Ser
Ala '	Ala	Pro	Ile 420	Gly	Ser	Gly	Glu	Asp 425	Glu	Val	Xaa	Gln	Thr 430	Ala	Ala
Arg	He	A1a 435	Gly	Ala	Leu	Gly	G1y 440	Leu	Leu	Thr	Pro	Leu 445	Phe	Leu	Arg
	Val 450	Leu	Ala	Tyr	Leu	I1e 455	Trp	Trp	Thr	Ala	A1a 460	Cys	Gln	Leu	Leu
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	_													atg Met		240	0
														cgg Arg 95		288	3
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Ser	Val	Thr	Gly 20		Gly	Phe	Ser	Va1 25		Asp	Leu	Ala	Pro 30	Pro	Arg		
Lys	Ala	Leu 35		Thr	Tyr	Pro	Lys 40		Ala	Gly	Glu	Met 45		Glu	Asp		
Gly			Arg	Phe	Leu	Cys 55	. •	Ser	Val	Phe	Ser 60		Gln	Val	Ala		
Ser	50 Thr	Leu	Lys	Gln	Val		His	Asp	Gln	G1n		Ala	Arg	Met	Glu		

469

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				aca Thr			Lys							336
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				cct Pro 135										432
				ggt Gly										480
				cag Gln					-	-	-		_	528
				cca Pro	_		His	-	-	_	_			576
				tct Ser										624
				ttt Phe 215										672
				gga Gly	-				-		-	•		720
		Ser		atg Met		Leu								768
	Leu			gct Ala	Thr					Asp				816

	-				gat Asp					-		_		864
-				_	gat Asp 295	-	 _				_	_	~	912
					aaa Lys					_			_	960
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					tgg Trp				_					1056
					ttg Leu									1104
					ctt Leu 375							-		1152
					ctc Leu			-	_	-	_	_	-	1200
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		Пe			cct Pro	Lys								1296
	Leu				ctg Leu									1344

472

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Lys Ala 225	Ala	Ser	Pro	Leu 230	Gly	Ser	Pro	Glu	Leu 235	Cys	Pro	Ser	Ala	Leu 240
His Gly	Leu	Ser	Gln		Mot	Lvc	ا اھ	Pro		Pro	Δla	Hic	Hic	
iiis uiy	Leu	JCI	245	Alu	1100	Lys	LCU	250	JCI	110	Alu	1113	255	LCu
Trp Ser	ا ا ا	1 211		Glu	Δla	Thr	Glv		۵ ا ا	Pho	Δsn	Leu		Pro
TIP Set	LCu	260	361	uiu	Alu	1111	265	Lys	110	THE	ДЭР	270	LCu	110
Asn Lys	110		۸ra	Lvc	۸cn	Lou		Lou	Tyr	110	San		دا۸	Lvc
ASII LYS	275	Ai y	Ai y	Lys	Ash	280	uiu	Leu	ועו	110	285	116	Aia	Ly3
Cys Leu		Clu	Mot	Thr	۸cn		۸cn	۸1 ء	Acn	۸۳۵		۸15	Cln	Val
-		GIU	net	1111	295	Ash	Ash	Ala	H211	300	Tie	Ата	dill	vai
290 Thr Lys		Acn.	110	C1		۸1 -	۸1 ¬	Dho	V-1		Lou	Tun	Lou	V-3
•	261	ASII	rie	310	Lys	Ala	АТа	rne	315	Lys	Leu	∤ y i	Leu	320
305	C1.u	۸۸۸	Dho		Lou	Val	۸cn	Lau		۸۵۵	Mat	Lou	۸۸۵	
Ser Gln	ч	Ary	325	Pro	Leu	Vai	H211		THE.	ASP	met	Leu	_	rne
Ala The	۸٦ -	W-1		۸٦.	Tun	۸٦.	۸۵۵	330	The	۸٦.	Dwa	1	335	1 011
Ala Thr	Ald		VdI	Ald	пр	Ald		пі5	Tur.	Ald	Pro		Leu	Leu
C1 I a	Can	340	C 0 10	Tmn	1	Doo	345	م زارا	C1	C1	۸	350	Doo	47.
Gly Leu		Ald	261.	пр	Leu		пр	П15	GIN	Giu		GIY	Pro	Ald
Clu Doo	355	Doo	Can	Dha.	Lau	360	۸	۲۵۵	Dwa	Mat	365	۸	V-1	Thus
Gly Pro		Pro	ser.	Prie		ыу	Arg	zer.	Pro		HIS	Arg	VdI	1 Hr.
370		Val	Lau	The	375	Lou	Dno	۸۵۵	C02	380	۸٦.	1	Lau	Lau
Leu Gln	GIU	Val	Leu		Leu	Leu	Pro	ASII		Met	Ald	Leu	Leu	
385	C1	Duna	T	390	C1	C1	The	C1	395	Dha	11.	۸۵۵	Т	400
Gln Lys	GIU	Pro		Lys	Giu	GIN	1nr		Lys	rne	rie	ASP	•	Leu
Dha Can	17.5	Mat	405	C 0 m	Dwa	مدا	C1	410	1	Can	, , [ ^	C1	415	A
Phe Ser	rie		GIU	zer.	Pro	Lys		Ald	Leu	ser.	Ald		ser.	Arg
Acn Lau	Lou	420	۸٦٥	The	Lou	Lou	425	Lou	۸۵۵	Val	Lou	430	C1	Dho
Asp Leu	435	Lys	Ald	1111	Leu	440	ser.	Leu	Arg	Vai	445		Giu	Prie
Luc Luc		<b>41</b> a	V-1	Tnn	The		۸1 م	Tun	C1.4	Tnn	445	•		
Lys Lys	Lys	Ald	Vai	пр		Arg	Ald	ıyı	GIY	•				
450					455					460				
,	210>	222												
	211>		:											
	212>		)											
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-	~13~	HUIIC	, sat	116118	,									
	220>													
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			-			gaa Glu	_		-				-	-		144
-	•					ggt Gly 55		_			-	-				192
~ ~						act Thr				_		_	_	_		240
-			-		-	tac Tyr	_		-	-	_				_	288
-						aca Thr							-			336
						gta Val		_				•		-		384
						cct Pro 135										432
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	-	Leu			gaa Glu											816
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-		-		_	gag Glu				_							1056

WO 01/29221

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•		•				ttt Phe			-	-		-		•	_	1200
-			-	_		ttt Phe			-		-	_		-	-	1248
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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
                    70
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Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
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Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
                    150
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Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
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Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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His	Gly	Leu	Ser	G1n 245	Ala	Met	Lys	Leu	Pro 250	Ser	Pro	Ala	His	His 255	Leu
Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	G1y 265	Lys	Ile	Phe	Asp	Leu 270	Leu	Pro
Asn	Lys	I1e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Пe	Ser 285	Пe	Ala	Lys
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305					310					315			Tyr		320
Ser	Gln	Gly	Arg	Phe 325	Pro	Leu	Val	Asn	Leu 330	Thr	Asp	Met	Leu	Ser 335	Val
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		355					360					365	Gly		
	370					375					380		Arg		
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Asp	Phe	Phe	Leu	Leu 405	Ile	Phe	Ala	Thr	Ala 410	Val	Val	Ala	Trp	Ala 415	Asp
			420				_	425					Leu 430		,
His	Gln	G1u 435	Asn	Gly	Pro	Ala	Gly 440	Pro	Val	Pro	Ser	Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	Gln	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
Asn 465	Ser	Met	Ala	Leu	Leu 470	Leu	Gln	Lys	Glu	Pro 475	Trp	Lys	Glu	Gln	Thr 480
G1n	Lys	Phe	He	Asp 485	Trp	Leu	Phe	Ser	Ile 490	Met	Glu	Ser	Pro	Lys 495	Glu
Ala	Leu	Ser	A1a 500	Gln	Ser	Arg	Asp	Leu 505	Leu	Lys	Ala	Thr	Leu 510	Leu	Ser
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Tyr	Gly 530	Trp													

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		_		-				_				_	tcg Ser	_	240
		_	_	-						-	-		gcc Ala 95	-	288
													gac Asp		336
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	-			-		-		_			_	-	atg Met		432

	Val					Pro			tgg Trp							480
									tca Ser 170							528
									ttc Phe							576
									tgc Cys							624
									ccc Pro				tga *			666
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Ser	Arg 50	Glu	Leu	Glu	Pro	Glu 55	Leu	Arg	Arg	Arg	Arg 60	Tyr	Glu	Tyr	Asp	
His 65		Asp	Ala	Ala	Ile 70		Gly	Phe	Arg	G1u 75		Glu	Lys	Ser	Arg 80	
	Ser	Glu	Ala	Ser 85		Ala	Пe	Leu	G1n 90		Val	Gln	Ala	Ala 95		
Phe	Gly	Pro	Gly 100		Thr	Leu	Leu	Ser 105	Ser	Val	His	Val	Leu 110		Leu	
Glu	Ala	Arg		Tyr	Ile	Lys	Pro		Val	Asp	Ser	Ile		Phe	Cys	

115 120 125 Gly Ala Thr Ile Ala Gly Leu Ser Leu Leu Ser Pro Ser Val Met Arg

	130					135					140					
Leu 145	Val	His	Thr	Gln	G1u 150	Pro	Gly	Glu	Trp	Leu 155	Glu	Leu	Leu	Leu	G1u 160	
Pro	Gly	Ser	Leu	Tyr 165	Ile	Leu	Arg	Gly	Ser 170	Ala	Arg	Tyr	Asp	Phe 175	Ser	
His	Glu	He	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
	_	195				Ser	200					205	Pro	Glu	Gly	
Met	Gly 210	Pro	Gly	Glu	Ser	Gly 215	Gln	Pro	Pro	Pro	Ala 220	Cys				
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						act Thr				_	-		_		-	144
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			-			gac Asp						-	-	_		240
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Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Glu Met Pro Gln 35 40 45

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 50 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 65 70 75 80
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Leu

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96

ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg Phe Cys Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

483

20 25 30 tgg aag ata aac aac ctc att gcc tca gaa tcc tac tac acc tac gcc 144 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 35 40 45 tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg 192 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 50 55 60 ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag 240 Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 75 80

gaa gcc gtg gag aga cag ttg atg acc tga 270 Glu Ala Val Glu Arg Gln Leu Met Thr \*

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 25
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 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala
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 Ser Ile Ser Gly Ile Ser Ser Met 50
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cgt gtt tat cct tcc tgc ctt gaa cct ggt cag agt ttt att act gag 96 Arg Val Tyr Pro Ser Cys Leu Glu Pro Gly Gln Ser Phe Ile Thr Glu 20 25 30

48

gaa gat gat gca cgg agt gag tot agt act gaa tgg gac tta gat gga 144 Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40

ttc agt gag ctg gac tct gag tca gga agt tca agt tct ttt tca gat 192 Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Phe Ser Asp 50 55

gat gaa gtc tgg gtg caa gta gca cct cag cga aat gca cag gat cag 240 Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln 65 70 75 80

255 cag ggt tct ttg taa Gln Gly Ser Leu \*

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485

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						tat Tyr									96
						cac His				_	-	-		-	144
						tat Tyr 55									192
						cat His									240
tag *															243

<210> 334

<211> 80

<212> PRT

<213> Homo sapiens

486

	<	400>	334													
Met 1	Glu	IJе	Leu	Trp 5	Leu	Met	۷aΊ	Lys	Ser 10	Trp	Asn	Thr	Gly	Val 15	Leu	
Met	Phe	Ser	Arg 20	Ser	Lys	Tyr	Ala	Ser 25	Ala	Glu	Lys	Trp	Cys 30	Gly	Leu	
Ala	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	Glu 45	Ser	Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	Glu 60	Ala	Leu	Ser	Asn	
Asn 65	Lys	Gly	Pro	Val	Phe 70	His	G1u	His	Gly	Tyr 75	Trp	Ser	Lys	Ser	Asp 80	
	<'¿	210> 211> 212> 213>	237	o sar	oiens	5										
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	<4	100>	335													
										tcc Ser						48
	-	_		-	_	-			-	ttc Phe	-		-	_	-	96
-	_	_		_	-		-			gtt Val			-	-		144
	-						_			caa G1n	_		-	_	_	192
										atg Met				tga *		237

<210> 336

487

<211> 78 <212> PRT <213> Homo sapiens <400> 336 Met Pro Val Val Leu Ser Gln Glu Val Glu Ser Val Leu Val Gly Ala 10 Ala Val Leu Gly Ala Cys Ala Ser Gly Asp Phe Ala Ser Val Gln Glu 25 Ala Met Ala Lys Met Ser Lys Val Gly Lys Val Val Phe Pro Arg Leu 35 40 45 Gln Asp Lys Lys Tyr Tyr Asp Lys Lys Tyr Gln Val Phe Leu Lys Leu 55 60 Val Glu His Gln Lys Glu Tyr Leu Ala Ile Met Asn Asp Asp 70 75 <210> 337 <211> 567 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(567) <400> 337 atg cac tot att otg gat att att got gga tto ota tat acc att tta 48 Met His Ser Ile Leu Asp Ile Ile Ala Gly Phe Leu Tyr Thr Ile Leu 1 10 ato the got git the tat coa tit gitg gad etg att gad aad tit aad 96 Ile Leu Ala Val Phe Tyr Pro Phe Val Asp Leu Ile Asp Asn Phe Asn 20 25 30 caa act cac aaa tat gct cca ttc atc atc atc ggg ctt cat tta gct 144 Gln Thr His Lys Tyr Ala Pro Phe Ile Ile Ile Gly Leu His Leu Ala 35 40 ttg ggg atc ttt tct ttc act ctt gac acc tgg agc aca tcc cga gga 192 Leu Gly Ile Phe Ser Phe Thr Leu Asp Thr Trp Ser Thr Ser Arg Gly 50 55 60 gac aca gcc gag ata cta gga agt ggt gct gga att gca tgt gga tct 240 Asp Thr Ala Glu Ile Leu Gly Ser Gly Ala Gly Ile Ala Cys Gly Ser

65					70					75					80	
	-	act Thr			-					-				-		288
		tta Leu	_								_				_	336
	_	cgg Arg 115					_	_		-				_	-	384
		aaa Lys								-						432
		gat Asp							-		_	-	-	-		480
		cgg Arg						-	-							528
		cct Pro														567
	<2 <2	210> 211> 212> 213>	188 PRT	sap	oiens	;										
Mo+		400>		Lou	۸cn	110	110	۸۱-	Clu	Dho	Lou	Tun	Thn	ī la	Lou	
1		Ser		5	•				10			_		15		
			20					25					30			
Gln	Thr	His 35	Lys	Tyr	Ala		Phe 40	Ile	He	Пe	Gly	Leu 45	His	Leu	Ala	
_eu	Gly	Пe	Phe	Ser	Phe	Thr	Leu	Asp	Thr	Trp	Ser	Thr	Ser	Arg	Gly	

	50					55					60					
Asp 65	Thr	Ala	Glu	He	Leu 70	Gly	Ser	Gly	Ala	Gly 75	Ile	Ala	Cys	Gly	Ser 80	
His	۷a۱	Thr	Tyr	Asn 85	Met	Gly	Leu	Val	Leu 90	Asp	Pro	Ser	Leu	Asp 95	Thr	
Leu	Pro	Leu	Ala 100	Gly	Pro	Pro	Ile	Thr 105	Val	Thr	Leu	Phe	Gly 110	Lys	Ala	
Ile	Leu	Arg 115	Ile	Leu	Пе	Gly	Met 120	Val	Phe	Val	Leu	Ile 125	Ile	Arg	Asp	
Val	Met 130	Lys	Lys	Ile	Thr	Ile 135	Pro	Leu	Ala	Cys	Lys 140	Ile	Phe	Asn	Ile	
Pro 145		Asp	Asp	Ile	Arg 150	Lys	Ala	Arg	Gln	His 155	Met	Glu	Val	Glu	Leu 160	
	Tyr	Arg	Tyr	Ile 165		Tyr	Gly	Met	Val 170	Gly	Phe	Ser	Ile	Thr 175	Phe	
Phe	Val	Pro	Tyr 180		Phe	Phe	Phe	Ile 185		Ile	Ser					
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	<2	220> 221> 222>		(2	210)											
-	gtt		cat		_	999 G1y			-		-				_	48
_				_		gtc Val	-		-							96
						gcg Ala										144
						gtg Val 55										192

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tac cta acc att ctt taa
                                                                      210
Tyr Leu Thr Ile Leu *
 65
      <210> 340
      <211> 69
      <212> PRT
      <213> Homo sapiens
      <400> 340
Met Val Ser His Phe Met Gly Ser Leu Ser Val Leu Cys Phe Leu Leu
                 5
                                    10
                                                         15
Leu Leu Gly Phe Gln Phe Val Cys Pro Gln Pro Ser Thr Gln His Arg
                                 25
Lys Val Pro Gln Arg Met Ala Ala Glu Gly Ala Pro Glu Asp Asp Gly
                            40
Gly Gly Gly Ala Pro Gly Val Trp Gly Ala Gly Ala Pro Ala Glu Gly
    50
                        55
Tyr Leu Thr Ile Leu
65
      <210> 341
      <211> 225
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(225)
      <400> 341
atg ccg gct aag gac aca agt tca gtg ttt gcc ctg gct tgt agc cca
                                                                       48
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
 1
                 5
                                      10
                                                          15
gcq ggg gct ccg tca tcc cct ggg gaa tgc ctc ggc ctg caa gac cgc
                                                                       96
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
                                 25
             20
                                                      30
                                                                      144
ata ccg cat tgg aac agg gaa acc acc tac ttc agc acc tcc ctc agc
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
```

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aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg
                                                                      192
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
     50
                         55
                                              60
                                                                      225
cat tcg gga tat ggc tcc ctg gcc agc ttg tga
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu *
 65
                     70
      <210> 342
      <211> 74
      <212> PRT
      <213> Homo sapiens
      <400> 342
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
                                25
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
                        55
                                            60
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu
65
                    70
      <210> 343
      <211> 240
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(240)
      <400> 343
atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc
                                                                       48
Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu
 1
                                     10
atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca
                                                                       96
Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr
             20
                                 25
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492

ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 35 40 45 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile \* 65 70 75 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 5 10 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 25 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 55 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 70 - 75 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 48 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 15 10

			caa Gln					9	96
			tct Ser					14	<sub>+</sub> 4
			tat Tyr 55					19	2
			gcc Ala					24	0
			tgc Cys				taa *	28	5

<210> 346

<211> 94

<212> PRT

<213> Homo sapiens

<400> 346

 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1
 Leu 5
 Leu 10
 Leu 15
 <td

<210> 347

<211> 474

<212> DNA

<213> Homo sapiens

<220> <221> CDS <222> (1)...(474) <400> 347 atg gag gcc ctg agg gcc cac gag gtc gcg ctc cgc ctg ctg 48 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu . 5 1 10 tgt agg ccg tgg gcc tcg cgc gcc gcc cgc ccc aag ccc agc gcc 96 Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala 20 tcg gag gtg ctg acg cgg cat ctg ctg cag cgg cgc ctg ccg cac tqq 144 Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp 35 45 acc tee tte tge gtg eee tae age gee gte ege aac gae eag tte gge 192 Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly 50 ctc tcg cac ttc aac tgg ccg gtg cag ggc gcc aac tac cac gtc ctg 240 Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu 65 70 75 80 cgc acc ggc tgc ttc ccc ttc atc aag tac cac tgc tcc aag gct ccc 288 Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro 85 tgg cag gac ctg gcc cgg cag aac cgc ttc ttc acg gcg ctc aag qtc 336 Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 100 105 • 110 gtc aac ctc ggt att cca act tta tta tat gga ctt ggc tcc tgg tta 384 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 115 120 ttt gcc aga gtc aca gag act gtg cat acc agt tat gga ccc ata aca 432 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 130 135 140 gtt tat ttt ctc aat aaa gaa gat gaa ggt gcc atg tat tga 474 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr \*

495

145 150 155 <210> 348 <211> 157 <212> PRT <213> Homo sapiens <400> 348 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu 5 10 Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly 55 Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro 90 Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 105 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 120 125 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 130 135 140 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 150 <210> 349 <211> 288 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(288) <400> 349 atg gcg aaa gca ctg att gtc att ttt agc agt cac tta agg cct ata 48 Met Ala Lys Ala Leu Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile

10

15

			aag Lys								96
			agg Arg								144
			ctc Leu 55								192
			tta Leu				-	_			240
			gga Gly	_					•	tga *	288

<210> 350

<211> 95

<212> PRT

<213> Homo sapiens

<400> 350

 Met Ala Lys Ala Leu Ile Val Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile 1
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90

<210> 351

<211> 165

<212> DNA

<213> Homo sapiens

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      <222> (1)...(165)
      <400> 351
atg tgc tcc atc ccc cgg cat ctg ctg cca ttg gtc ctg cct gtt gcg
                                                                      48
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
 1
                 5
                                     10
                                                         15
tta ctt ctc tgt gcc ctg gag ccc ctc aag cac aga ggc ctc gaa agg
                                                                      96
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
             20
                                 25
                                                     30
ttg atc aga cat cct cag cac ctg gag cgg ggc ctg gca cac aag acg
                                                                     144
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
         35
                             40
gca atg aac ggc caa ccc tag
                                                                     165
Ala Met Asn Gly Gln Pro *
     50
      <210> 352
      <211> 54
      <212> PRT
      <213> Homo sapiens
      <400> 352
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
                               25
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
        35
                            40
                                                45
Ala Met Asn Gly Gln Pro
   50
      <210> 353
      <211> 159
      <212> DNA
     <213> Homo sapiens
      <220>
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<221> CDS
      <222> (1)...(159)
      <400> 353
atg tgc ttg agg gtt ttc acc ctg gcc ctc agt tgc ctg ctg tgc ggg
                                                                       48
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                       96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
             20
                                 25
                                                      30
                                                                      144
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
                             40
                                                  45
                                                                      159
cgt gtc ggg ctt tga
Arg Val Gly Leu *
     50
      <210> 354
      <211> 52
      <212> PRT
      <213> Homo sapiens
      <400> 354
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                                    10
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                25
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
        35
                                                45
Arg Val Gly Leu
    50
      <210> 355
      <211> 210
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(210)
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-	ggt	_	355 atg Met			_				_		_	-		-	. 48
			gtg Val 20		-			-				_				96
	_	_	gca Ala	-		-		_				_				144
_		_	gaa Glu		_	_					-			_		192
	-		tca Ser	_	tag *											210
	<2 <2	210> 211> 212> 213>	69	o sap	oiens	5										
		100>														
Met 1	Gly	Ala	Met	Asn 5	His	Asp	Thr	Asn	Tyr 10	Ser	Phe	Gln	Val	G1n 15	Cys	
Gly	Leu	Пe	Va1 20	Val	Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His	
Phe	Met	Asp 35	Ala	Glu	Leu	Cys	Ser 40		Tyr	Trp	Thr	Lys 45		Leu	Leu	
Arg	Leu 50		Glu	Tyr	Thr	Glu 55		Lys	Lys	Asn	G1n 60	. •	Ile	Gln	Lys	
Pro 65		Tyr	Ser	Glu		00					00					
	<2 <2	210> 211> 212> 213>	243	sap	oiens	;										

500

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      <222> (1)...(243)
      <221> misc feature
      <222> (1)...(243)
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atg gtc ctg ccg gtg gca gcc tat ggn ctg atc ctg atg gcc atg ctg
                                                                       48
Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
 1
                 5
                                                          15
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                       96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
             20
                                 25
                                                      30
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                         55
                                             60
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
                                                                      240
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
65
                     70
                                         75
                                                             80
                                                                      243
tga
```

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<210> 358
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<220>

<221> VARIANT

<sup>&</sup>lt;211> 80

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;223> Xaa = Any Amino Acid

	<	400>	358													
Met 1	Val	Leu	Pro	Val 5	Ala	Ala	Tyr	Xaa	Leu 10	Ile	Leu	Met	Ala	Met 15	Leu	
Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Aļa	Gly	Trp	Gly	A1a 30	Leu	Leu	
Phe	Thr	Leu 35	Ser	Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45	Ala	Gln	Pro	
Leu	Pro 50	His	Ala	Arg	Leu	Va1 55	Ile	Met	Thr	Thr	Tyr 60	Tyr	Ala.	Ala	Gln	
Leu 65	Leu	Ile	Thr	Leu	Ser 70	Αla	Leu	Arg	Ser	Pro 75	Val	Pro	Lys	Thr	Asp 80	
	<2 <2	210> 211> 212> 213>	324	o sap	oiens	5										
	<2	220> 221> 222>	CDS	(3	324)											·
atg		100> agc		tgt	ggt	tcc	ctt	gtg	gcc	atg	agt	gtt	gtg	gtg	gga	48
Met 1	Lys	Ser	Thr	Cys 5	Gly	Ser	Leu	Val	Ala 10	Met	Ser	Val	Val	Val 15	Gly	
	-		_	-		-	_	_	_		_			act Thr	-	96
											_	-		cgt Arg		144
-	-	_	-				_			-	_		-	gac Asp		192
														gga Gly	_	240
agt	tgg	gca	gga	aga	ctc	att	ctg	agt	gta	gat	ggc	tct	<b>g</b> gg	ttt	tgt	288

```
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                 85
                                                         95
                                                                      324
gag agg gtg aaa tot ttg gto gtt aaa caa tto tag
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
                 5
 1
                                    10
Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
                        55
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
                  · 70
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                                    90
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
      <210> 361
      <211> 252
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(252)
      <400> 361
                                                                       48
atg gag gaa gga ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                                     10
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
                                                                       96
```

503

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg		
							gac Asp 40									]	144
							aca Thr							-	_	1	192
		-		-			gca Ala			-						2	240
	aaa Lys		taa *													2	252

<210> 362

<211> 83

<212> PRT

<213> Homo sapiens

<400> 362

<210> 363

<211> 459

<212> DNA

<213> Homo sapiens

<	220> 221> 222>	CDS	(	459)											
gat		aca										gag Glu			48
 										_		tat Tyr 30			90
				-		-	-		-			cct Pro		_	144
												atg Met			192
			_		_				_			999 Gly	-	•	. 240
									Ala			aga Arg			288
												ttg Leu 110			336
								_		-		aac Asn		_	384
								-		_	_	gaa Glu	_		432
		-			tgt Cys	-	tag *								459

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<210> 364
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      <213> Homo sapiens
      <400> 364
Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu
                                     10
Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
                        55
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
                                         75
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
                                     90
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
            100
                                 105
                                                     110
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
                                                 125
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
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Phe Gly Glu Val Lys Ser Cys Leu
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ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
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Phe	Gly	Leu	Ser 20		Val	Tyr	Phe	Leu 25		Ser	Thr	Phe	Lys 30		Glu	
			Val								gtt Val					144
		He									ggc Gly 60					192
											aag Lys					240
gat Asp	gaa Glu	ctc Leu	ggc Gly	tac Tyr 85	gtt Val	tgc Cys	gag Glu	agg Arg	aag Lys 90	gat Asp	ttg Leu	ctg Leu	gta Val	aat Asn 95	ggc Gly	288
											tac Tyr					336
											tac Tyr					384
											cgc Arg 140				cgg ' Arg	432
											gtc Val					480
								Thr			cag Gln					528
gag Glu							Ile				tgc Cys					576
ccg	ccc	gag	ctc	ttc	ccc	gct	tga									600

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Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
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Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
                        55
                                            60
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
                                        75
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
                                    90
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                                105
            100
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                            120
                                                125
Cys Leu Gln Pro Asn Lys Gln Leu Leu Leu Glu Arg Phe Leu Asn Arg
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                                            140
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
                    150
                                        155
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
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                165
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
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Pro Pro Glu Leu Phe Pro Ala
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508

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249

agt gga tga Ser Gly \*

<210> 368

<211> 82

<212> PRT

<213> Homo sapiens

<400> 368

 Met
 Ser
 Lys
 Tyr
 Lys
 His
 Lys
 Ser
 Ser
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 Leu
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 Leu
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Ala
 Asn
 Lys
 Pro
 Leu
 Ala
 Asn
 Lys
 Pro
 Lys
 Ile
 Leu
 Ala
 Ala
 Cys
 Leu
 Glu
 Ser
 Glu
 Asn
 Asn
 Asn
 Ala
 Ala
 Ala
 Leu
 Glu
 Leu
 Glu
 Asn
 Asn
 Leu
 Glu
 Lys
 Pro
 Ile
 Glu
 Asn
 Ser
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 Lys
 Lys</th

509

Ser Gly

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Pro	Pro	A1 a 35	Pro	Gln	Asn	Pro	G1y 40	Gly	Ser	Thr	Gln	A1a 45	Pro	Gln	Arg	
Val	Va1 50	Gly	Lys	Ser	His	Ser 55	Gly	Ile	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
Asn 65	Leu	Arg	Leu	Glu	Ser 70	Lys	Leu	Asn	Arg	Thr 75	Ala	Val	Cys	G1u	A1a 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 90	Gly	Val	Gly	Ser			
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		Phe	Asp	Glu	Lys	Tyr	Lys	Pro	Val	gtg Val	Leu	Thr	Asp			144
										ttg Leu						192
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.ca	ลดล	taa														2/10

511

Pro Arg \*

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<211> 82

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<213> Homo sapiens

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His Leu Arg Val Val Gly Pro Gln Gln Leu His Ser Glu Thr Asn Glu 20 25 30

Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35 40 45

Val Asp Gln Ala Leu Trp Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50 55 60

Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65 70 75 80 Pro Arg

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Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Ser Ala His

20

25

30

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Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
         35
                                                 45
                                                                     192
gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga
Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
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aat acc acg cac tgc ccc ttc gcc tag
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Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
Glu Pro Arg Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
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Asn Thr Thr His Cys Pro Phe Ala
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144		_	-	ttg Leu 45	-	_										
192				tgc Cys												
240		-		gcc Ala	_										Trp	
288				ctc Leu												
336				cct Pro												
384				gtg Val 125												
432	gcg Ala	999 Gly	999 G1y	tgg Trp	atg Met 140	999 Gly	tat Tyr	act Thr	aac Asn	gcc Ala 135	acg Thr	ttc Phe	gtc Val	gct Ala	gta Val 130	att []e
480				gag Glu												
528				ttg Leu												

514

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
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tga

170

175

576

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<400> 376

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185

Met Ala Pro Lys Pro Gly Ala Glu Trp Ser Thr Ala Leu Ser His Leu

<210> 377

180

<211> 606

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												gtg Val		. 96
						-	-			_		agg Arg		144
								_	_			gcc Ala	_	192
												ggc Gly		240
									_		_	cag Gln 95		288
												acc Thr		336
											_	ctg Leu		384
												caa Gln		432

	Ser		gtc Val													480
			aac Asn													528
			acg Thr 180													576
			act Thr	_					tga *							606
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1	Thr	Val	Gln	5					10					15		
1	Thr	Val	Gln Leu	5				Ala	10				Trp	15		
1 Ser	Thr Leu	Val Ile Leu	Gln	5 Asn	Asn	Val	Ala Arg	A1a 25	10 Phe	Thr	Ser	Asn Leu	Trp 30	15 Val	Cys	
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1 Ser Gln Cys	Thr Leu Thr Trp 50	Val Ile Leu 35 Leu	Gln Leu 20 Glu	5 Asn Asp Asp	Asn Gly Arg	Val Arg Thr 55	Ala Arg 40 Arg	Ala 25 Arg Gly	10 Phe Ser Gly	Thr Val Pro	Ser Gly Ser 60	Asn Leu 45 Pro	Trp 30 Trp Gly	15 Val Arg Ala	Cys Ser Arg	
1 Ser Gln Cys Ala 65	Thr Leu Thr Trp 50 Gly	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val	5 Asn Asp Asp	Asn Gly Arg Ala 70	Val Arg Thr 55 His	Ala Arg 40 Arg Asp	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu	Thr Val Pro Ala 75	Ser Gly Ser 60 Leu	Asn Leu 45 Pro Gly	Trp 30 Trp Gly Trp	15 Val Arg Ala Gly	Cys Ser Arg Ser 80	
1 Ser Gln Cys Ala 65	Thr Leu Thr Trp 50 Gly	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val	5 Asn Asp Asp	Asn Gly Arg Ala 70	Val Arg Thr 55 His	Ala Arg 40 Arg Asp	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu	Thr Val Pro Ala 75	Ser Gly Ser 60 Leu	Asn Leu 45 Pro Gly	Trp 30 Trp Gly Trp	15 Val Arg Ala Gly	Cys Ser Arg Ser 80	
1 Ser Gln Cys Ala 65 Glu	Thr Leu Thr Trp 50 Gly	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val Val Gly Arg	5 Asn Asp Asp Asp Phe 85	Asn Gly Arg Ala 70 Gln	Val Arg Thr 55 His Glu	Ala Arg 40 Arg Asp Ser	Ala 25 Arg Gly Cys Arg	10 Phe Ser Gly Glu Gly 90	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys	Trp 30 Trp Gly Trp Leu Leu	15 Val Arg Ala Gly Gln 95	Cys Ser Arg Ser 80 Phe	
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1 Ser Gln Cys Ala 65 Glu Asp	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp	Val Ile Leu 35 Leu Gln Ala Met Leu 115	Gln Leu 20 Glu Val Val Gly Arg 100	5 Asn Asp Asp Asp Phe 85 Ala	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu	Ala Arg 40 Arg Asp Ser Leu Gly 120	Ala 25 Arg Gly Cys Arg Val 105 Leu	10 Phe Ser Gly Glu Gly 90 Ala	Thr Val Pro Ala 75 Thr Thr	Ser Gly Ser 60 Leu Val Ala Leu	Asn Leu 45 Pro Gly Lys Ala Pro 125	Trp 30 Trp Gly Trp Leu Leu 110 Leu	15 Val Arg Ala Gly Gln 95 Thr	Cys Ser Arg Ser 80 Phe Ala	
1 Ser Gln Cys Ala 65 Glu Asp Gly Pro	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp 130	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe Cys	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu 135	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu Ala	10 Phe Ser Gly Glu Gly 90 Ala Val	Thr Val Pro Ala 75 Thr Chr Ala	Ser Gly Ser 60 Leu Val Ala Leu Ala 140	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala	Trp 30 Trp Gly Trp Leu 110 Leu Phe	15 Val Arg Ala Gly Gln 95 Thr Leu Gln	Cys Ser Arg Ser 80 Phe Ala Ser Leu	
1 Ser Gln Cys Ala 65 Glu Asp Gly Pro Ala 145	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp 130 Ser	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	Asp Asp Asp Asp Phe 85 Ala Phe Cys Leu	Asn Gly Arg Ala 70 Gln Cys Leu Trp Val 150	Val Arg Thr 55 His Glu Asn Leu Glu 135 Ile	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu Ala	10 Phe Ser Gly Glu Gly 90 Ala Val Met	Thr Val Pro Ala 75 Thr Gly Ala Thr 155	Ser Gly Ser 60 Leu Val Ala Leu Ala 140 Phe	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala Tyr	Trp 30 Trp Gly Trp Leu 110 Leu Phe Arg	15 Val Arg Ala Gly Gln 95 Thr Leu Gln Ile	Cys Ser Arg Ser 80 Phe Ala Ser Leu Gly 160	

				165					170					175		
Leu	Leu	Ala	Thr 180			Ala	Ala	Cys 185	Ser	Ser	Gly	Thr	Phe 190	Ser	Thr	
Arg	Gly	Arg 195	Thr	Ala	Trp	Pro	Pro 200	Gly								
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								aga Arg 25				_	-		-	96
								gag Glu						-		144
								gca Ala					-			192
								tgt Cys								240
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act ggt tag
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Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
                        55
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
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Thr Gly
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1
                 5
                                     10
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						aaa Lys										144
						gag Glu 55										192
						agc Ser										240
	gga Gly					aag Lys	tga *									264
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Leu	Phe	Leu	Thr 20	Cys	Tyr	Ala	Asp	Asp 25	Lys	Pro	Asp	Lys	Pro 30	Asp	Asp	
Lys	Pro	Asp 35	Asp	Ser	Gly	Lys	Asp 40		Lys	Pro	Asp	Phe 45		Lys	Phe	
Leu	Ser 50		Leu	Gly	Thr	G1u 55		Ile	Glu		Ala 60		Glu	Phe	He	
65	Arg				70	Ser	Thr	Gly	Phe			Phe	Asp	Asp	Asn 80	
GIU	Gly	Lys	нтѕ	Ser 85	ser	Lys										
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520

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Val Leu Pro Glu Gln Glu Thr Pro Arg Glu

70

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521

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															96
														-	144
_	-		_				-	-	-	_	_	•	-	-	192
		-	_	-	_	_			-				_	_	240
														tga *	288
	ctg Leu gcc Ala gac Asp 50 aag Lys	<211> <212> <213> <220> <221> <222> <221> <222> <223> <400> gcc ccc Ala Pro  ctg ctg Leu Leu  gcc gag Ala Glu 35  gac tgc Asp Cys 50  aag aca Lys Thr  gca gag	<211> 288 <212> DNA <213> Hom <220> <221> CDS <222> (1) <222> mis <222> (1) <223> n = <400> 385 gcc ccc ccg Ala Pro Pro  ctg ctg ctg Leu Leu Leu 20 gcc gag ccc Ala Glu Pro 35  gac tgc cac Asp Cys His 50  aag aca gcc Lys Thr Ala  gca gag cgc	<220> <221> CDS <222> (1)(  <221> misc_fe <222> (1)(  <223> n = A.T  <400> 385 gcc ccc ccg cnc Ala Pro Pro Xaa  5  ctg ctg ctg ctg Leu Leu Leu Leu 20  gcc gag ccc gcc Ala Glu Pro Ala 35  gac tgc cac gcc Asp Cys His Ala 50  aag aca gcc tgc Lys Thr Ala Cys  gca gag cgc cgt Ala Glu Arg Arg	<211> 288 <212> DNA <213> Homo sapien <220> <221> CDS <222> (1)(288) <221> misc_feature <222> (1)(288) <223> n = A.T.C or <400> 385 gcc ccc ccg cnc gcg Ala Pro Pro Xaa Ala 5  ctg ctg ctg ctg ctg ctg Leu Leu Leu Leu Leu 20  gcc gag ccc gcc ggg Ala Glu Pro Ala Gly 35  gac tgc cac gcc ttc Asp Cys His Ala Phe 50  aag aca gcc tgc agc Lys Thr Ala Cys Ser 70  gca gag cgc cgt gcc Ala Glu Arg Arg Ala	<211> 288 <212> DNA <213> Homo sapiens  <220> <221> CDS <222> (1)(288)  <221> misc_feature <222> (1)(288) <223> n = A.T.C or G  <400> 385 gcc ccc ccg cnc gcg tnc Ala Pro Pro Xaa Ala Xaa 5  ctg ctg ctg ctg ctg ctg ctg Leu Leu Leu Leu Leu Leu Leu 20  gcc gag ccc gcc ggg agt Ala Glu Pro Ala Gly Ser 35  gac tgc cac gcc ttc gag Asp Cys His Ala Phe Glu 50  aag aca gcc tgc agc ctg Lys Thr Ala Cys Ser Leu 70  gca gag cgc cgt gcc ctg Ala Glu Arg Arg Ala Leu	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;221&gt; misc_feature &lt;222&gt; (1)(288) &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg Ala Pro Pro Xaa Ala Xaa Arg 5  ctg ctg ctg ctg ctg ctg ctg agt Leu Leu Leu Leu Leu Leu Ser 20  gcc gag ccc gcc ggg agt gcc Ala Glu Pro Ala Gly Ser Ala 35</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;221&gt; misc_feature &lt;222&gt; (1)(288) &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc Ala Pro Pro Xaa Ala Xaa Arg Ser 5  ctg ctg ctg ctg ctg ctg agt ctg Leu Leu Leu Leu Leu Leu Ser Leu 20 25  gcc gag ccc gcc ggg agt gcc gtc Ala Glu Pro Ala Gly Ser Ala Val 35 40  gac tgc cac gcc ttc gag ttc atg Asp Cys His Ala Phe Glu Phe Met 50 55  aag aca gcc tgc agc ctg gac gcg Lys Thr Ala Cys Ser Leu Asp Ala 70  gca gag cgc cgt gcc ctg tgt gcc Ala Glu Arg Arg Ala Leu Cys Ala</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;221&gt; misc_feature &lt;222&gt; (1)(288) &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg Ala Pro Pro Xaa Ala Xaa Arg Ser Pro 5 10  ctg ctg ctg ctg ctg ctg agt ctg gcg Leu Leu Leu Leu Leu Leu Ser Leu Ala 20 25  gcc gag ccc gcc ggg agt gcc gtc ccc Ala Glu Pro Ala Gly Ser Ala Val Pro 35 40  gac tgc cac gcc ttc gag ttc atg cag Asp Cys His Ala Phe Glu Phe Met Gln 50 55  aag aca gcc tgc agc ctg gac gcg cgg Lys Thr Ala Cys Ser Leu Asp Ala Arg 70  gca gag cgc cgt gcc ctg tgt gcc tgc Ala Glu Arg Arg Ala Leu Cys Ala Cys</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1) (288)  &lt;221&gt; misc_feature &lt;222&gt; (1) (288) &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg atg Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt;</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;222&gt; (1)(288)  &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg atg tca ccn Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;221&gt; misc_feature &lt;222&gt; (1)(288) &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg atg tca ccn cng Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa 5</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;222&gt; misc_feature &lt;222&gt; (1)(288)  &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg atg tca ccn cng ncg Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa 5 10 15  ctg ctg ctg ctg ctg ctg agt ctg gcg ctg ggg gcc cgg Leu Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg 20 25 30  gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro 35 40 45  gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp 50 55 60  aag aca gcc tgc agc ctg gac gcg gcg acg gag acc cta ctg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu 70 75  gca gag cgc cgt gcc ctg tgt gcc tgc tgg cca gcg ggg cac Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His</pre>	<pre>&lt;211&gt; 288 &lt;212&gt; DNA &lt;213&gt; Homo sapiens  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(288)  &lt;221&gt; misc_feature &lt;222&gt; (1)(288)  &lt;223&gt; n = A.T.C or G  &lt;400&gt; 385 gcc ccc ccg cnc gcg tnc cgg tcc ccg atg tca ccn cng ncg nng Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa Xaa 5 10 15  ctg ctg ctg ctg ctg ctg agt ctg gcg ctg ggc gcc cgg gcc Leu Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala 20 25 30  gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca tgc Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys 35 40 45  gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac ctg Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu 50 55 60  aag aca gcc tgc agc ctg gac gcg gcg gcg gag gac ctt ctg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu 70 75 80  gca gag cgc cgt gcc ctg tgt gcc tgc tgc tgg cca gcg ggg cac tga Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His *</pre>

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<211> 95

<212> PRT

<213> Homo sapiens

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Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
                            40
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
                        55
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
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Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His
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                85
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      <400> 387
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 1
                 5
                                     10
                                                         15
gtg ttt gtt ttc ctg gga aac tcc agc tgc gct ccg cag aga ctg ttg
                                                                       96
Val Phe Val Phe Leu Gly Asn Ser Ser Cys Ala Pro Gln Arg Leu Leu
             20
                                 25
                                                                      144
gag aga agg aac tgg act cct caa gct atg ctc tac ctg aaa ggg gca
Glu Arg Arg Asn Trp Thr Pro Gln Ala Met Leu Tyr Leu Lys Gly Ala
        35
                             40
                                                 45
cag ggt cgc cgc ttc atc tcc gac cag agc cgg aga aag gac ctc tcc
                                                                      192
Gln Gly Arg Arg Phe Ile Ser Asp Gln Ser Arg Arg Lys Asp Leu Ser
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523

50 55 60 240 gac egg eca etg eeg gaa aga ega age eea aat eee eaa eta eta aet Asp Arg Pro Leu Pro Glu Arg Arg Ser Pro Asn Pro Gln Leu Leu Thr . 65 70 75 80 att ccg gag gca gca acc atc tta ctg gcg tcc ctt cag aaa tca cca 288 Ile Pro Glu Ala Ala Thr Ile Leu Leu Ala Ser Leu Gln Lys Ser Pro 85 90 gaa gat gaa gaa aaa aac ttt gat caa acc aga ttc ctg gaa gac agt 336 Glu Asp Glu Glu Lys Asn Phe Asp Gln Thr Arg Phe Leu Glu Asp Ser 100 105 110 351 ctg ctt aac tgg tga Leu Leu Asn Trp \* 115 <210> 388 <211> 116 <212> PRT <213> Homo sapiens <400> 388 Met Lys Gly Leu Arg Ser Leu Ala Ala Thr Thr Leu Ala Leu Phe Leu 5 10 Val Phe Val Phe Leu Gly Asn Ser Ser Cys Ala Pro Gln Arg Leu Leu 25 20 -30 Glu Arg Arg Asn Trp Thr Pro Gln Ala Met Leu Tyr Leu Lys Gly Ala 40 Gln Gly Arg Arg Phe Ile Ser Asp Gln Ser Arg Arg Lys Asp Leu Ser 55 Asp Arg Pro Leu Pro Glu Arg Arg Ser Pro Asn Pro Gln Leu Leu Thr 75 70 80 Ile Pro Glu Ala Ala Thr Ile Leu Leu Ala Ser Leu Gln Lys Ser Pro 90 Glu Asp Glu Glu Lys Asn Phe Asp Gln Thr Arg Phe Leu Glu Asp Ser 100 105 110 Leu Leu Asn Trp 115 <210> 389

<211> 318

524

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<212> PRT

<213> Homo sapiens

<400> 390

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Asp	Phe	Lys 35	Tyr	Ala	Leu	Ile	Gly 40		Ala	Val	Gly	Val 45		Ile	Ser	
Ala	Gly 50		Leu	Ala	Leu	Lys 55	Пe	Cys	Met	Пe	Arg 60		His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70		Lys	Ser	Thr	Pro 75		Gly	Leu	Ser	Asp 80	
Thr	Пe	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95		
Lys	Arg	Asp	Ala 100	Gln	Val	Ile	Glu	Leu 105								
	<'¿	212>	391 150 DNA Home	sa <sub>l</sub>	piens	S										
	<2		CDS (1)	(:	150)											
	<2	222>	miso (1) n =	(1	150)											
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			ccc Pro 20													96
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gcc Ala	taa *														•	150

526

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527

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 60 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 65 70 75 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 85 95 ttc tga 294 Phe \* <210> 394 <211> 97 <212> PRT <213> Homo sapiens <400> 394 Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Leu 5 10 Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg 25 Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 60 55 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 65 70 75 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 90 85 Phe <210> 395

<211> 303 <212> DNA <213> Homo sapiens <220> <221> CDS

528

<222> (1)...(303)

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Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
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Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
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Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met
                                  90
Glu Asn Glu Thr
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      <212> DNA
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      <220>
      <221> CDS
      <222> (1)...(141)
      <400> 397
48
Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn
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                5
                                   10
                                                      15
ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg
                                                                  96
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
            20
gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga
                                                                 141
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu *
        35
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                                              45
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     <211> 46
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     <213> Homo sapiens
     <400> 398
Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn
1
                5
                                  10
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
                              25
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu
       35
                          40
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	<'	220> 221> 222>		(;	360)										
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_		-	-			_		cct Pro 25				-		-	96
								gcc Ala							144
		-	_					agc Ser		-	-	-	_		192
	-			_		-		cat His	-				-		240
								999 Gly							288
-								cat His 105	-						336
		aac Asn 115					tga *								360

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Ala Ser Met Ala Glu Asn Ser Ile Pro Leu Tyr Thr Thr Ala Ser Met
                                 25
Gly Asn Pro Thr Leu Gly Asn Leu Ala Ser Ala Ile Arg Glu Glu Leu
                             40
                                                 45
Asn Gly Ala Met Glu His Thr Asn Ser Asn Glu Ser Asp Ser Ser Pro
                        55
Gly Arg Ser Pro Met Gln Ala Val His Pro Val His Val Lys Glu Glu
                    70
                                         75
Pro Leu Asp Pro Glu Glu Ala Glu Gly Pro Leu Ser Leu Val Thr Thr
                                     90
Ala Asn His Ser Pro Asp Phe Asp His Asp Arg Asp Tyr Glu Asp Glu
            100
                                 105
Pro Val Asn Glu Asp Met Glu
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      <211> 474
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      <400> 401
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Met Ser Lys Ser Cys Gly Asn Asn Leu Ala Ala Ile Ser Val Gly Ile
 1
                                      10
                                                          15
tcg ctt ctt tta ctc tta gtg gtt tgt gga att ggg tgt gtt tgg cac
                                                                       96
Ser Leu Leu Leu Leu Leu Val Val Cys Gly Ile Gly Cys Val Trp His
             20
                                 25
                                                      30
tgg aaa cac cgt gtt gcc aca cga ttt acc tta ccg agg ttt tta caa
                                                                      144
Trp Lys His Arg Val Ala Thr Arg Phe Thr Leu Pro Arg Phe Leu Gln
         35
                             40
                                                 45
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	Ile					cat His					Glu					240
						aat Asn									Val	288
						gct Ala										336
						aat Asn										384
						aac Asn 135										432
						tac Tyr							tag *			474
	<2 <2	?10> ?11> ?12> ?13>	157	sap	oi ens	i									·	
Mo+		00>		C	C1	A	A	<i>.</i>	A 7 .	4.7	•	•		0.7		
1				5		Asn			10					15		
Ser	Leu	Leu	Leu 20	Leu	Leu	Val	Val	Cys 25	Gly	He	Gly	Cys	Val 30	Trp	His	
Trp		His 35	Arg	Val	Ala	Thr	Arg 40	Phe	Thr	Leu		Arg 45	Phe	Leu	Gln	
Arg	Arg 50	Ser	Ser	Arg		Lys 55	Val	Cys	Thr	-			Leu	Gly	Pro	

533 Arg Ile Ile Gly Leu Arg His Glu Ile Ser Val Glu Thr Gln Asp His 65 70 75 Lys Ser Ala Val Arg Gly Asn Asn Thr His Asp Asn Tyr Glu Asn Val 90 Glu Ala Gly Pro Pro Lys Ala Lys Gly Lys Thr Asp Lys Glu Leu Tyr 105 Glu Asn Thr Gly Gln Ser Asn Phe Glu Glu His Ile Tyr Gly Asn Glu 120 115 Thr Ser Ser Asp Tyr Tyr Asn Phe Gln Lys Pro Arg Pro Ser Glu Val 130 135 140 Pro Gln Asp Glu Asp Ile Tyr Ile Leu Pro Asp Ser Tyr 145 150 155 <210> 403 <211> 279 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(279) <400> 403 atg tgg cct gtg ttt tgg acc gtg gtt cgt acc tat gct cct tat gtc 48 Met Trp Pro Val Phe Trp Thr Val Val Arg Thr Tyr Ala Pro Tyr Val 1 5 15 96 aca ttc cct gtt gcc ttc gtg gtc ggg gct gtg ggt tac cac ctg gaa Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30 tgg ttc atc agg gga aag gac ccc cag ccc gtg gag gaa aag agc 144 Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 atc tca gag cgc cgg gag gat cgc aag ctg gat gag ctt cta ggc aag 192 Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

gac cac acg cag gtg gtg agc ctt aag gac aag cta gaa ttt gcc ccg Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro

75

70

aaa gct gtg ctg aac aga aac cgc cca gag aag aat taa

65

240

534

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn \* 85 90

<210> 404

<211> 92

<212> PRT

<213> Homo sapiens

<400> 404

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Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30

Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 45

Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 80

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn 85 90

<210> 405

<211> 255

<212> DNA

<213> Homo sapiens

<220>

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48

96

cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc Gln Pro Lys Arg Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20 25 30

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt
Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser
35 40 45

535

gga atg aat toa gtt agc too att cag aac caa atg cag too aag gga 192 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 50 ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat 240 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 75 80 acg aag gcg gga tag 255 Thr Lys Ala Gly \* <210> 406 <211> 84 <212> PRT <213> Homo sapiens <400> 406 Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 25 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 40 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 60 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 75 80 Thr Lys Ala Gly <210> 407 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 407

536

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		_												tgt Cys		144
		_	_						_	-			_	gtt Val		192
_			-	_	-		-	-	-	-	-	-	-	aat Asn	-	240
	agc Ser	-														249
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Arg Ile Leu Asn Thr Gly Leu Asp Met Glu Thr Leu Ser Ile Cys Val 35 40 45

Arg Leu Cys Glu Gln Gly Ile Asn Pro Glu Ala Leu Ser Ser Val Ile

Lys Glu Leu Arg Lys Ala Thr Glu Ala Leu Lys Ala Ala Glu Asn Met 65 70 75 80

Thr Ser

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                 5
                                      10
 1
                                                          15
ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                       96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
             20
                                 25
                                                      30
act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
                                                                      144
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
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                                                 45
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Leu Arg Val *
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Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
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WO 01/29221

538

PCT/US00/29052

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			ctg gac agg Leu Asp Arg 60		
		Asp Phe Gly	cag ttg gcc Gln Leu Ala 75		
			gac ttc tgg Asp Phe Trp 90		
Leu Thr Gln			gac att ttg Asp Ile Leu S	-	
			atc act ggt (		-
gcg ttg cac	atc cta aag	ttt gaa gag	tct aaa taa		420

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Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys *
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Thr Leu Ala Gln Ala Glu Glu Gln Gln Pro Tyr Leu Glu Gly Ser Thr
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Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
                        55
Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
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Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
                                105
                                                     110
Val Val His Arg Ile Leu Lys Gly Lys Ile Thr Gly Ala Leu Asn Ser
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                                                125
Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys
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			ctt Leu	-		-	-									192
			tca Ser		-					_	-				•	240
			aag Lys							-					-	288
			aag Lys 100			-	_		_						_	336
			gcc Ala	_	-		_			-	-				_	384
cgt Arg		-	ctg Leu	_		-	_									432
		_	caa Gln		-	_					•	•				480
gaa Glu			gaa Glu				_			-		_	-			528

	tgt Cys														_	576
	agc Ser	_			_						_	-			-	624
	gaa Glu 210		-					-				-				672
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Asp	Leu	Ile 35		Ser	Thr	Leu	Asn 40		Ser	Lys	Ile	G1y 45		Phe	Tyr	
Thr	Asp 50		Leu	Val	Pro	Met 55	Val	Gly	Asn	Asn	Pro 60	Tyr	Ala	Thr	Thr	
Glu 65	Gly	Asn	Ser	Thr	G1u 70		Ser	Пe	Asn	A1a 75	_	Val	Tyr	Ser	Leu 80	
	Ser	Arg	-	Leu 85	-	Ala	Leu	Gln	Leu 90		Ser	Ile	Phe	Ile 95		
Tyr	Lys	Ser			Phe	Cys	Glu	Lys		Leu	Ser	Trp	Val		Ser	

			100					105					110			
Ser	Gly	Cys 115	Ala	Arg	Val	Ile	Val 120	Leu	Ser	Ser	Ser	His 125	Ser	Tyr	Gln	
Arg	Asn 130	Asp	Leu	Gln	Leu	Arg 135	Ser	Thr	Pro	Phe	Arg 140	Tyr	Leu	Leu	Thr	
Pro 145	Ser	Met	Gln	Lys	Ser 150		Gln	Asn	Lys	I 1e 155	Lys	Ser	Leu	Asn	Trp 160	
Glu	Glu	Met	Glu	Lys 165	Ser	Arg	Cys	Ile	Pro 170	Glu	Ile	Asp	Asp	Ser 175	Glu	
Phe	Cys	Ile	Arg 180	Ile	Pro	Gly	Gly	Gly 185	Ile	Thr	Lys	Thr	Leu 190	Tyr	Asp	
G1u	Ser	Cys 195	Ser	Lys	Glu	Ile	G1n 200	Met	Ala	Val	Leu	Leu 205	Lys	Phe	Val	
Ser	G1u 210	Gly	Asp	Asn	Ile	Pro 215	Asp	Ala	Leu	Gly	Leu 220	Val	Glu	Tyr	Leu	
Asn 225	Glu	Trp	Leu	Gln	Ile 230	Leu	Lys	Pro	Leu	Ser 235	Asp	Asp	Pro	Thr	Va1 240	
Ser	Ala	Ser	Arg	Trp 245	Lys	Пe	Pro	Ser	Ser 250	Trp	Arg	Leu	Leu	Phe 255	Gly	
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	ctc Leu													-		96
	atg Met															144

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                                                                       192
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                                              60
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Ile Met Arg Arg Ser Pro Leu Ala Val Ala Gly Phe Gln Asp Gly Gly
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Ser Val Asp Ser Lys Glu Met Arg Thr Gln
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 1
                                     10
cag cta tta atg tca tgt ccc caa gtt gaa tta att cag tgt ctc act
                                                                       96
Gln Leu Leu Met Ser Cys Pro Gln Val Glu Leu Ile Gln Cys Leu Thr
             20
                                 25
                                                     30
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					gca Ala	-	-			-			-			192
					ggt Gly 70							_		_		240
					tcc Ser											288
-		-			ttt Phe	-					-		_			336
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Gln	Leu	Leu	Met 20	Ser	Cys	Pro	Gln	Va1 25	Glu	Leu	Ile	Gln	Cys 30	Leu	Thr	
Lys	Glu	Leu 35		Glu	Lys	Gln	Pro 40		Leu	Ser	Phe	G1y 45		Ala	Ile	
Leu	His 50		Phe	Ser	Ala	Asp 55		Lys	Lys	Val	Gly 60		Lys	Leu	Leu	
Gln		Πe	Asn	Lvs	Gly		Ile	Asp	Ala	Val		Ser	Leu	Met	Ile	

65					70					75					80	
Asn	Asp	Ser	Phe	Cys 85	Ser	Ile	Glu	Lys	Trp 90	Gln	Glu	Val	Ala	Asn 95	Ile	
			Asn 100					105			•		110			
Leu	Arg	Ser 115	Gln	Ala	Ala	۷a۱	Thr 120		Ile	Ser	Glu	G1u 125	Asp	Asp	Ala	
Val	Asn 130	Leu	Met	Glu	His	Val 135		Trp								
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			cat His 20									-	-			96
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			atg Met													192
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546

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50 55 60

tgg aag ctg cag gat ggc tgc agg ggg ccg tgg acc ctc ctg gcc tga 240
Trp Lys Leu Gln Asp Gly Cys Arg Gly Pro Trp Thr Leu Leu Ala \*
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Trp Val Cys Trp Glu Pro Gly Ile Thr Gly Cys Arg Pro Gln Arg Lys 20 25 30

Val Pro Glu Asp Thr Val Pro Lys Ser Asp Pro Arg Gly Gly Arg Lys 35 40 45

Val Gly Arg Gly Glu Gly Leu Ser Ala Gly Met Val Gl<br/>n Glu Glu Asp  $50 \hspace{1.5cm} 55 \hspace{1.5cm} 60$ 

Trp Lys Leu Gln Asp Gly Cys Arg Gly Pro Trp Thr Leu Leu Ala 65 70 75

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Glu Tyr Met Pro Met Glu

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